

# ANNALS OF INTERNAL MEDICINE

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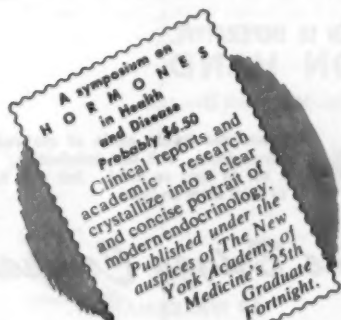
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2. Humphreys, P., et al.: Angiology 3:1 (Feb.) 1952.
3. Plotz, M.: New York State J. Med. 52:2012 (Aug. 13) 1952.

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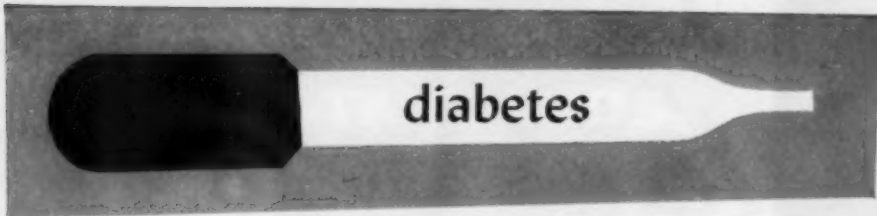
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2. Steine, L.: *GP* 8:45 (July) 1953.

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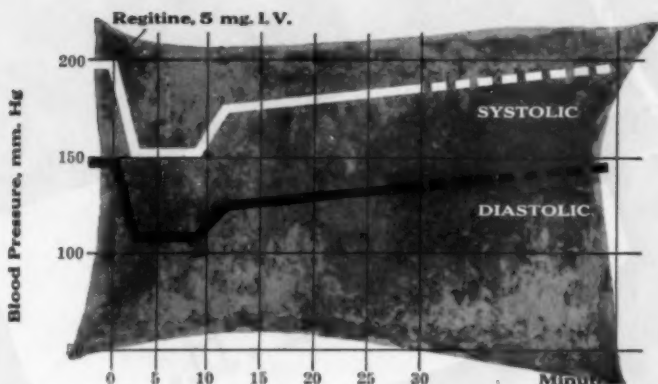
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"... the most effective of all antihistamines and has the highest degree of safety . . ."<sup>1</sup>

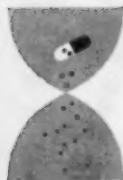
A single dose of one 'Teldrin' *Spansule* capsule provides a continuous and sustained antihistamine effect over a period of 10-12 hours.


*Smith, Kline & French Laboratories, Philadelphia*

1. Margolin, S., and Tislow, R.: Experimental and Clinical Efficacy of Trimeton and Chlor-Trimeton Maleate, Ann. Allergy 8:515, 1950.

<sup>\*</sup>Trademark

<sup>†</sup>Trademark for S.K.F.'s brand of sustained release capsules (patent applied for).





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1. Pollock, B. E., and Pruitt, F. W.; Am. J. M. Sc. 226:172, 1953.



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Unitensen (Irwin-Neisler) is the only product which  
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The results obtained [with Unitensen] in  
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\*Carotid Sinus Reflex

1. Finnerty, F. A.: Hypertensive Encephalopathy. GP (in Press).

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1. McHardy and Browne: *Sou. M.J.* 45:1139, 1952.

2. Lorber and Shay: *Fed. Proc.* 12:90, 1953.

Complete Bentyl bibliography on request.

T.M. 'Bentyl'

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Pyridoxine Hydrochloride.....	1 mg.
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**ACTION:** Hexamethonium therapy produces parasympathetic as well as sympathetic blockade. The former is reflected in the hypertensive patient as side effects including nausea, constipation, and paralytic ileus. URECHOLINE has been reported to be the most satisfactory parasympathomimetic agent<sup>1</sup> for overcoming undesirable and sometimes grave side-effects. This drug is also most valuable for urinary retention, another hexamethonium-induced side-effect. Its use increases patient cooperation and permits the continued administration of hexamethonium compounds. URECHOLINE

is valuable given either to *prevent* the appearance of advanced hexamethonium-induced side-effects or to *control* such disturbances.

1. Freis, E.D., Finnerty, F.A., Jr., Schnaper, H.W., and Johnson, R.L.: *Circulation* 5:20, Jan. 1952.

**SUPPLIED:** 5-mg. tablets, bottles of 100; 1-cc. ampuls containing 5-mg. each of URECHOLINE Chloride.

COUNCIL  ACCEPTED

# What about Cobalt?

## —in anemia—

Q. Why is Roncovite\* effective in anemias of bone marrow depression due to infection or disease?

A. Because cobalt is the only agent known which, by stimulating erythropoiesis, will cause the hemopoietic system to utilize the iron already available to it.

Q. Why use cobalt in iron-deficiency anemia—isn't iron alone adequate?

A. Roncovite is preferentially indicated in ALL forms of "secondary" or iron-deficiency anemia for the following reasons:

Many so-called iron-deficiency anemias are in reality a combination of an iron-deficiency and an inhibition of hemopoiesis *resulting from long continued extra drain* on the bone marrow.

With iron alone,<sup>1</sup> therefore, a complete clinical response is often difficult or impossible to obtain—only very small gains or poor responses being frequently reported in "low-grade anemias."

Roncovite, by providing the added bone marrow (red cell) stimulant action of cobalt, will supply that added extra "push" to mobilize iron reserves, produce a faster response, greatly superior erythropoiesis and up to fourfold increases in the utilization of iron.<sup>2</sup>

Q. Why is iron present in Roncovite?

A. The increased hemopoiesis from the specific bone marrow stimulant action of cobalt often creates a need for additional iron to make hemoglobin for the new red cells—Roncovite provides iron to fill this need and to maintain iron reserves.

Q. Can I be sure that cobalt is safe for routine use?

A. Cobalt is an essential element with a low order of toxicity—no greater than that of iron. A cobalt chloride dosage of as high as



1200 mg. per day, in divided doses, has produced no severe toxic effects even if continued for six weeks.<sup>3</sup> This is equivalent to a daily dosage of over 80 Roncovite tablets.

**Q. Is cobalt cumulative?**

- A. No—extensive pharmacological investigation proves that cobalt is rapidly and almost completely excreted via the urine<sup>4</sup> so that there is little if any cumulative effect even after periods exceeding 100 days of continuous parenteral use. The body shows no significant amounts of cobalt 48 hours after the last dose.<sup>4</sup>

**Q. Is the improvement with Roncovite noticeably rapid?**

- A. Yes—the patient often voluntarily reports an increased sense of well-being within a few days—as reported by documented clinical evidence.

Roncovite is not indicated in pernicious or megaloblastic anemia.

**HOW SUPPLIED:**

**Roncovite Tablets**—enteric coated, red, each contains cobalt chloride, 15 mg.; exsiccated ferrous sulfate, 0.2 Gm.; bottles of 100. Dose: One tablet 4 times a day.

**Roncovite Drops**—each 0.6 cc. contains cobalt chloride, 40 mg.; ferrous sulfate, 75 mg.; bottles of 15 cc. with calibrated dropper. Dose: 0.6 cc. daily.

# RONCOVITE

The First True Hematopoietic Stimulant

1. Cass, L. J.; Frederick, W. S., and DiGregorio, S.: *Journal-Lancet* 51:73 (1953).
2. Rohn, R. J., and Bond, W. H.: *Journal-Lancet* 73:317 (1953).
3. Berk, W., et al.: *New England J. M.* 240:754 (May) 1949.
4. Berlin, N. I.: *J. Biol. Chem.* 187:41 (1950).

\*The original Cobalt-Iron Product.

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Together with significant reductions in elevated blood pressure in 80 per cent of hypertensives,<sup>1,2</sup> Methium therapy may produce an appreciable improvement in the associated renal symptoms when actual uremia is not present. Albuminuria and hematuria present in 48 of the 120 hexamethonium-treated patients followed by Moyer's group, improved definitely in 28 cases.<sup>1</sup> In addition, progressive renal failure did not continue so long as the blood pressure was controlled.

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1. Moyer, J. H.; Miller, S. I., and Ford, R. V.: J.A.M.A. 152:1121 (July 18) 1953.

2. Moyer, J. H.; Snyder, H. B.; Johnson, I.; Mills, L. C., and Miller, S. I.: Am. J. M. Sc. 225:379 (April) 1953.

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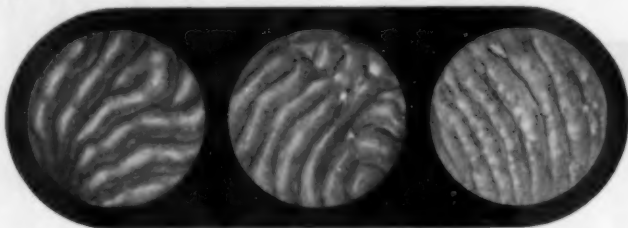
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Tablets, 5 grain, boxes of 30, bottles of 100;  
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1. Hollander, F.: Arch. Int. Med. 93:107 (Jan.) 1954



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...is based on the use of 1) azopyrine\*, 2) ACTH or cortisone and 3) psychotherapy."

"Azopyrine\* ... has been effective in controlling the disease in approximately two-thirds of patients who had previously failed to respond to standard colitis therapy currently in use."

1. Rev. Gastroenterology 20:744 (Oct.) 1953; abstract in J. A. M. A., 153:1580 (Dec. 26) 1953.

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### Reports on Azulfidine:

(This drug has been presented under three different names, which appear in the literature cited, viz: Salazopyrin, Azopyrin and the now established name in America, Azulfidine.)

1949 "The administration of salicylazosulfapyridine (salazopyrin) produced marked improvement in 8 of 12 cases of ulcerative colitis."

Bargen, J. A.: Med. Clin. North America, 33:935 (July) 1949.

1950 Bargen reports that since 1949 approximately 100 patients have been treated with Azulfidine. "The results have been extremely satisfactory in most cases."

Personal communication (Apr. 12)

1951 After-control data 1949 from 119 patients treated with Azulfidine prior to 1944 showed 90 patients (84%) symptom-free or considerably improved.

Svartz, N.: Acta Med. Scandinav. 141:172, 1951.

1952 In a series of 52 patients with chronic ulcerative colitis 30 or 58% showed significant improvement after treatment with Azulfidine.

Morrison, L. M.: Gastroenterology 21:133, 1952.

1953 Morrison publishes results from a series of 47 patients treated with Azulfidine compared to a control series of 60 patients receiving other current therapy: In the Azulfidine-series 18% are symptom-free and 52% improved, compared to 5% and 32% respectively, in the control series.

J. A. M. A.: 151:366 (Jan. 31) 1953.

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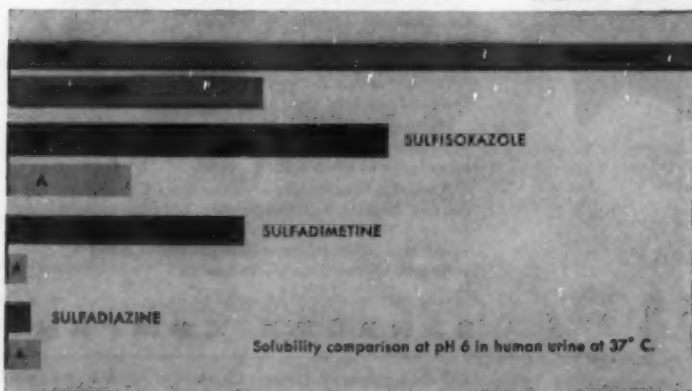
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Each Semhyten Capsule contains:	Phenobarbital.. ¼ gr. (15 mg.)
Mannitol Hexanitate... ½ gr. (30 mg.)	Rutin ..... 10 mg.
Theophylline ..... 1 ½ gr. (0.1 Gm.)	Ascorbic Acid ..... 15 mg.

Supplied: In bottles of 100, 500 and 1000 pink-top capsules.

The S. E. MASSENGILL Company • Bristol, Tennessee

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*NOW: for Adults and Children!*

**Nephenalin<sup>®</sup>**

(for adults)



**Nephenalin<sup>®</sup>**

**PEDIATRIC**



**First, under tongue for**  
**quick asthma relief**

*from aludrine (Isopropyl arterenol) HCl in coating*

**Then, swallow tablet for**  
**prolonged asthma control**

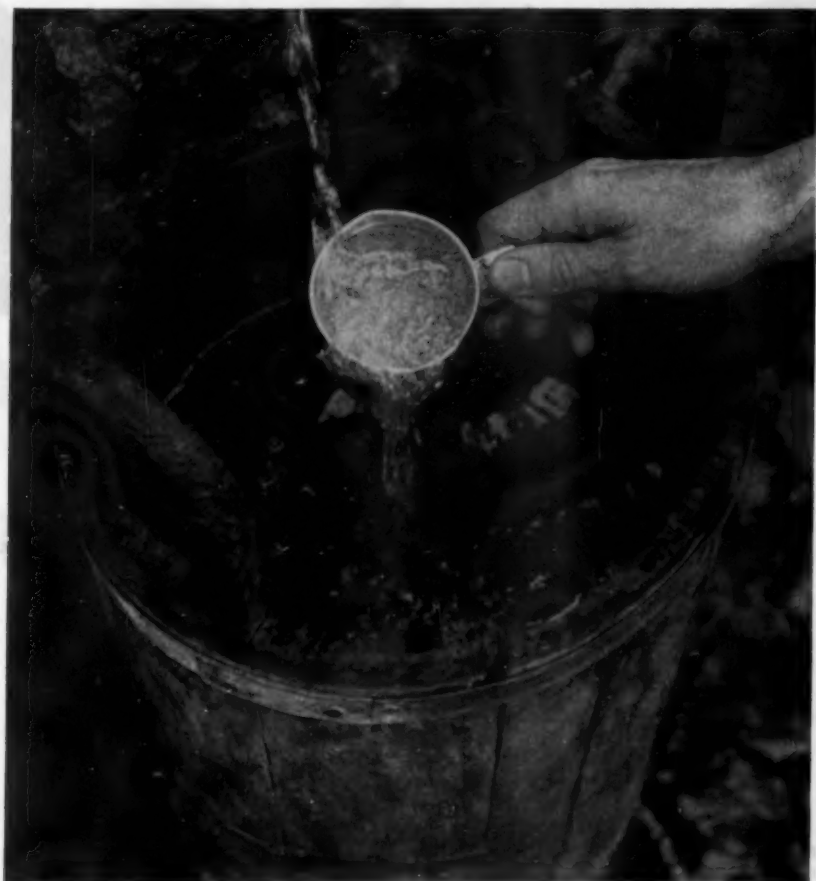
*from theophylline, ephedrine, phenobarbital, contained in tablet core*

NEPHENALIN, the "relay-action" tablet combining two widely prescribed, complementary anti-asthmatics, is now available in two potencies: the familiar square, *purple* tablet for adults, and the smaller square, *red* tablet for children. Since a single NEPHENALIN tablet provides quick asthma relief, thereby often replacing the nebulizer, and since relief lasts about four hours, many asthmatic patients will find it the most convenient and efficient anti-asthmatic they have ever used. Bottles of 20 and 100 tablets.

*Thos. Leeming & Co. Inc.* 155 East 44th St., New York 17

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### Picturesque

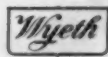
Yes, but it could be a reservoir of diarrheal infection. Against the common diarrheas, STREPTOMAGMA brings potent antibacterial action *plus* adsorbent, demulcent and protective effects. Clinical experience with STREPTOMAGMA indicates that remission is nearly always prompt and complete.



## STREPTOMAGMA<sup>®</sup>

*Dihydrastreptomycin Sulfate and  
Pectin with Kaolin in Alumina Gel*

Bottles of 3 fl. oz.



Philadelphia 2 Pa.



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# Have you tasted Meritene Doctor?

One taste tells the story. Here is the high protein nourishment patients will delight in drinking... the sure route to *extra* nutrition whenever required, for all ages.

Let us send *you* a one pound can for your own taste-test.



**HIGH PROTEIN** Supplementation  
**and it tastes good**

## MERITENE vs. EGGNOG Nutritive Value Comparison

	EGGNOG	MERITENE MILK SHAKE
Protein.....	12.5 gm.	15.8 gm.
Fat.....	12.6 gm.	8 gm.
Carbohydrate.....	17.7 gm.	25.5 gm.
Calcium.....	.24 gm.	.5 gm.
Phosphorus.....	.27 gm.	.4 gm.
Iron.....	1.5 mg.	4.4 mg.
Vitamin A.....	843 I.U.	1745 I.U.
Thiamine.....	.12 mg.	.7 mg.
Riboflavin.....	.45 mg.	1.6 mg.
Ascorbic Acid....	2.0 mg.	26.4 mg.
Cholesterol.....	288 mg.	21 mg.
Calories.....	233	237

Eggnog nutritive values from "Food Values of Portions Commonly Used." Bowes & Church, 1951.



**INSTITUTIONAL SIZE PRICE**  
(in 100 pound quantities)—99¢ per pound

In the management of medical and surgical convalescence, debilitating diseases, geriatric nutritional imbalance...you immediately seek to increase the patient's protein intake.

More and more physicians are finding the answer in MERITENE—the fortified whole protein supplement that patients *like to take*. Its good taste assures that.

Therapeutic values abound in a Meritene Milk Shake: high quality protein without the burden of bulk...more of all other important vitamins and minerals than in an equal amount of Eggnog. Yet Meritene Milk Shakes cost *less*. Write for a full one pound can . . . or

### MAIL THIS COUPON

#### THE DIETENE COMPANY

MI 54

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I am interested in becoming more familiar with MERITENE. Please send me FREE a one pound can so that I can try it.

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CITY \_\_\_\_\_ ZONE \_\_\_\_\_ STATE \_\_\_\_\_



**Dainite tablets** meet the distinct difference in drug requirement of the active and resting asthmatic patient. Clearly marked to preclude confusion, the Dainite *night* tablets contain more aminophylline and sedative to compensate for the elimination of ephedrine, and assure a restful night. An effective and prolonged dosage of aminophylline protected by anti-nausea factors has been given without gastric side effects to hundreds of patients with gratifying results.<sup>1-5</sup>

- References:** (1) Segal, M. S., et al.: *Quart. Rev. Allergy & Applied Immunol.* 6: 399-415, 1952; (2) Barach, A. L.: *Med. Rec. & Ann.* 46: 323-331, 1952; (3) Segal, M. S., et al.: *Trans. Nat. The. Assn.*, 48th Ann. Meet., 1952, pp. 374, 385; (4) Segal, M. S., and Dulfano, M. J.: *GP* 7: 58, 1953; (5) Segal, M. S., and Dulfano, J. M.: *Modern Med. Monographs*, New York, Grune & Stratton, 1953, No. 8, pp. 79-80.

### *In bronchial asthma*

**Dainite  
tablets**

Each DAY Tablet  
contains:

.... Phenobarbital .....	1/4 gr.
1/4 gr. .... Sodium Pentobarbital .....	1/2 gr.
3 gr. .... Aminophylline .....	4 gr.
1/4 gr. .... Ephedrine HCl .....	
1/4 gr. .... Ethyl Aminobenzoate .....	1/4 gr.
2 1/2 gr. .... Aluminum Hydroxide .....	2 1/2 gr.

Give 1 i.d.s.c.

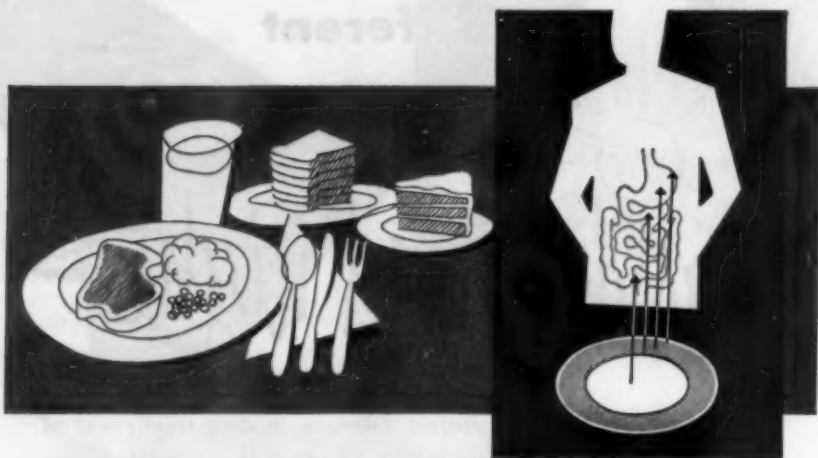
Each NIGHT Tablet  
contains:

Give at 10 P.M.



Supplied in bottles of 50 Day tablets and 50 Night tablets; also supplied as the Dainite Unit containing 48 Day tablets and 12 Night tablets in a unique dispensing package.

**IRWIN, NEISLER & COMPANY • DECATUR, ILLINOIS**



*effective aid to digestion  
and assimilation of foods*

## CONVERTIN<sup>®</sup>

*Special layered construction  
ensures separately timed action  
of essential digestants for  
maximum therapeutic effect*

Each CONVERTIN tablet provides:  
a sugar-coated outer layer containing  
Betaine Hydrochloride . 130.0 mg.  
(Equiv. 5 minims Diluted Hydrochloric Acid U.S.P.)  
Oleoresin Ginger . . . . . 1/600 gr.  
surrounding an enteric-coated core of  
Pancreatin . . . . . 62.5 mg.  
(Equiv. 250 mg. U.S.P.)  
Desoxycholic Acid . . . . . 80.0 mg.  
Chlorophyllin . . . . . 10.0 mg.

DOSAGE: 2 tablets with or just after meals; clinical experience has shown that dose may be reduced, usually after first week, at physician's discretion.

**B. F. ASCHER & COMPANY, INC.**

Ethical Medicinals  
KANSAS CITY, MO.



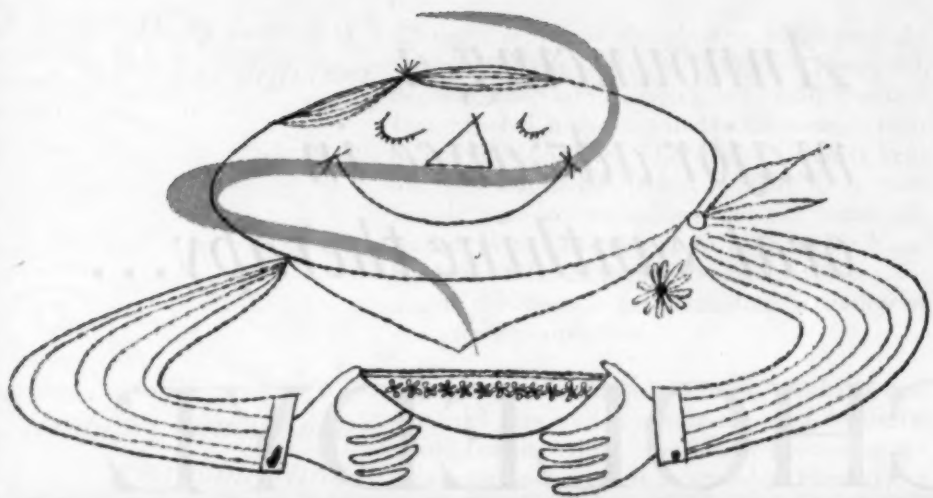
### *digestant tablets*

*Convertin* aids protein digestion through the release of HCl from betaine hydrochloride and through the subsequent action of the pancreatic enzyme, trypsin.

*Convertin* aids carbohydrate digestion through the action of the pancreatic enzyme, amylase.

*Convertin* aids fat digestion through the action of desoxycholic acid (a pure bile acid) and the pancreatic enzyme, steapsin. And for patient-comfort... CONVERTIN contains the carminative, oleoresin ginger.

Available on prescription at  
leading pharmacies in  
bottles of 84 and 500 tablets.



## salt-free needn't mean flavor-free

DIASAL is enthusiastically endorsed by low-salt dieters for the zest and flavor it gives to pallid, sodium-restricted meals. So closely does it match the appearance, texture and taste of table salt that patient adherence to your diet instructions is virtually assured.

DIASAL contains only potassium chloride, glutamic acid and inert ingredients—no sodium, lithium, or ammonium. It may be used safely for extended periods, both at the table and in cooking. Because of its potassium, DIASAL may be a valuable prophylactic against potassium depletion.

## DIASAL®

packaging: available in 2-ounce shakers and 8-ounce bottles.  
Send for liberal supplies of testing samples and low-sodium diet sheets for your patients.



**FOUGERA**

**E. FOUGERA & COMPANY, INC.**  
75 Varick Street, New York 13, N. Y.

*Announcing a  
major advance in  
oral xanthine therapy...*

# CHOLEDYL<sup>®</sup>

(Choline Theophyllinate, NEPERA)

- ...five times more soluble than oral aminophylline
- ...provides theophylline blood levels up to 76% higher than does oral aminophylline  
(the therapeutic effect of aminophylline is due solely to its theophylline content)
- ...free of the common gastric irritations associated with oral aminophylline

It is now possible to build, and to maintain, uniformly high theophylline blood levels by the oral route. With just 200 mg. of new oral Choledyl q.i.d. you can provide continuous diuretic, vasodilator and bronchodilator xanthine effects — in a long-range effort to forestall severe attacks, rather than await their random occurrence.

Comparative theophylline  
blood levels (mg.%)  
after a single oral dose  
(800 mg.) of Choledyl  
and aminophylline





### *Why Choledyl is different*

Choledyl is a new theophylline derivative—the theophylline salt of choline. In this new compound, decomposition into irritating and highly insoluble free theophylline is prevented by the strongly basic quaternary choline. The theophylline is kept ionized—a state in which it is many times more soluble than aminophylline, and far better absorbed. With Choledyl, up to 76% higher blood levels are obtained than with aminophylline, yet it avoids the common gastrointestinal irritation of ordinary aminophylline.

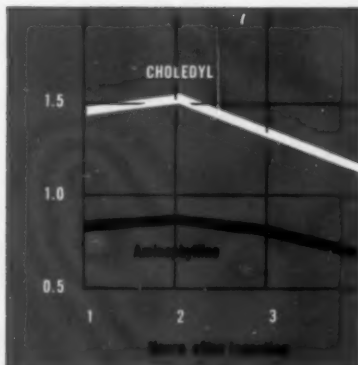
### *Does Choledyl replace intravenous aminophylline?*

Administered routinely, on a day-by-day basis, oral Choledyl may well eliminate the need for intravenous aminophylline injection by preventing the appearance of severe acute episodes. However, if such episodes do occur, intravenous aminophylline should still be considered.

### *Designed for continuous, intensive therapy*

Oral Choledyl is designed for continuous, intensive theophylline medication free from the drawbacks of (a) poorly soluble, irritating aminophylline, orally; (b) scattered emergency use of aminophylline, intravenously.

The objectives of Choledyl medication reach beyond an emergency situation. They are: *planned* diuresis, *prolonged* coronary vasodilation, *continued* relief of bronchospasm. Unlike aminophylline, no loss of efficacy is observed during prolonged therapy with Choledyl.



## CHOLEDYL®

(Choline Theophyllinate, NEPERA)

**Dose:** *Adults*—initiate with 200 mg. q.i.d. Adjust dosage to individual requirements. *Children over six:* 100 mg. t.i.d. or q.i.d.

**Important:** In many patients, the most pronounced effect appears after Choledyl has been given continuously for some time. If the desired results do not appear quickly, dosage should be continued for more prolonged periods.

**Supplied:** 100 mg. and 200 mg. tablets; bottles of 100 and 500.

NEPERA CHEMICAL CO. INC.  
Pharmaceutical Manufacturers  
Nepera Park, Yonkers 2, N. Y.





a new drug for



## PARKINSONISM

Orally administered Parsidol is effective in modifying or controlling symptoms of parkinsonism such as akinesia, tremor, spasm, festination, sialorrhea, oculogyric crises, and extrapyramidal hypertonicity.<sup>1</sup> Besides its high degree of effectiveness against the neuromuscular manifestations of parkinsonism (favorable responses in 60-80% of cases), Parsidol markedly improves depressed attitudes common in the disease.<sup>2</sup>

This effectiveness, while dependent upon the individual case and necessary dosage regulation, is often superior to that of comparable agents.<sup>1</sup> In addition, Parsidol has produced particularly noteworthy responses when administered with

other adjunctive drugs.<sup>3</sup> The value of such combined therapy lies in the enhancement of Parsidol's effect on a specific symptom and in controlling the few side effects of the drug.

Available in 10 mg. and 50 mg. tablets in bottles of 100 and 500. Trial supplies of 10 mg. tablets and complete information on Parsidol will be sent promptly when requested.

### References:

1. Sigwald, J.: Presse méd. 59:819 (Sept. 17) 1949.
2. Gallagher, D. J. A., and Palmer, H.: New Zealand M. J. 49:531 (Oct.) 1950.
3. Timberlake, W. H., and Schwab, R. S.: New England J. Med. 247:98 (July 17) 1952.

# PARSIDOL®

HYDROCHLORIDE

[Brand of N-(2-diethylaminopropyl)-phenothiazine hydrochloride]

**WARNER-CHILCOTT**  
*Laboratories* NEW YORK



**carsickness**

**control**

**for young**

**and old**

*with new  
long acting*

**Bonamine\***

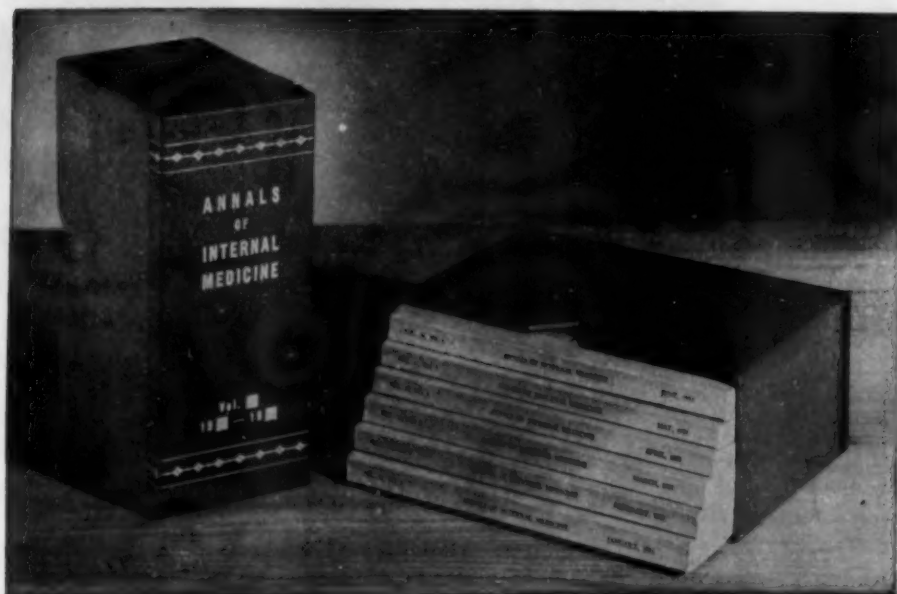
Brand of meclizine

Prevention of carsickness and all types of motion sickness is simplified and improved with this effective new agent. A single daily dose of one to two 25 mg. tablets for adults (less for children) taken one hour before the start of a trip ordinarily provides 24-hour protection against the nausea and vomiting associated with motion sickness. Side effects, often noted with use of other remedies, are minimized with Bonamine. In bottles of 25 mg. scored, tasteless tablets.

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## RAPID CURES

**of urinary tract infections  
prevent permanent kidney damage**

Infections of the lower urinary tract rarely remain localized for any length of time. The kidneys are often invaded rapidly unless effective treatment is instituted immediately. Hence, the choice of the first drug used may decide the fate of the kidneys.

# FURADANTIN<sup>®</sup>

brand of nitrofurantoin, Eaton

Furadantin is unique, a new chemotherapeutic molecule, neither a sulfonamide nor an antibiotic.

**RAPID ACTION.** Within 30 minutes after the first Furadantin tablet is taken, the invaders are exposed to antibacterial urinary levels.

**WIDE ANTIBACTERIAL RANGE.** Furadantin is strikingly effective against a wide range of clinically important gram-negative and gram-positive bacteria, including strains notorious for high resistance.

Scored tablets of 50 mg.



Bottles of 50 and 250.

Scored tablets of 100 mg.



Bottles of 25 and 250.



Also available: Furadantin Pediatric Suspension, containing 5 mg. of Furadantin per cc. Bottle of 4 fl. oz.

THE NITROFURANS—  
A UNIQUE CLASS  
OF ANTIMICROBIALS  
PRODUCTS OF  
EATON RESEARCH



**EATON**  
LABORATORIES  
NORWICH, NEW YORK

**SODIUM  
RESTRICTED**  
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Add tasty salads and casserole dishes to sodium restricted diets with Cellu Canned Tuna and Salmon. Packed in distilled water without added salt or oil. Food values printed on each label.



**CELLU BONED CHICKEN**—For many flavorful salads and hot dishes. Packed unsalted, boned, ready for use. Only 34.4 mg. sodium in 100 grams. In 5 oz. tins.

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**DOCK\***  
**BALLISTOGRAPH**



\*As described by William Dock, M.D., et al. Vol. 140, No. 14, Aug. 4, 1951, Jt. A. M. A. Ballistocardiography in Med. Proc.

Compact design, engineered for accuracy, simplicity of use and clinical efficiency. No service required. Records on any make ECG. Simultaneous QRS reading. **\$50.00** F.O.B. NEW YORK

With "leg block" carrying case—\$12.50 extra

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**A safer tranquilizer-antihypertensive**

**No other rauwolfia product offers such**

**Unvarying potency / Accuracy in dosage / Uniform results**

**Serpasil**  
(reserpine Ciba)

*A pure crystalline alkaloid of Rauwolfia serpentina*

**C I B A**

Tablets 0.25 mg. and 0.5 mg.

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When the infection is a  
gram-negative bacillus,  
anticipate susceptibility to

There are many reports  
of infections with  
these bacilli, which  
have continued to  
exacerbate in spite of  
other therapy, until  
administration of  
'Aerosporin' has brought  
about remission and  
early clearing.

**'AEROSPORIN'®**

Sulfate

*Polymyxin B Sulfate*



#### How Supplied

*For intramuscular or intrathecal administration:*

'AEROSPORIN' Sterile, 500,000 Units, equivalent  
to 50 mg. Polymyxin Standard  
vial of 20 cc. capacity

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to 20 mg. Polymyxin Standard  
vial of 20 cc. capacity

*For oral administration:*

'AEROSPORIN' Compressed, Scored,  
500,000 Units, equivalent  
to 50 mg. Polymyxin Standard  
Foil-wrapped in boxes of 12

#### Bibliography:

1. Frank, P.F., Wilcox, C., and Finland, M.: In Vitro Sensitivity of Coliform Bacilli to Seven Antibiotics. *J. Lab. & Clin. Med.* 35:188 and 305, 1950.
2. Jawetz, E. and Coleman, V.R.: Laboratory and Clinical Observations on Aerosporin (Polymyxin B). *J. Lab. & Clin. Med.* 34:731, 1949.
3. Pulaaki, E.J. and Rosenberg, M.L.: Use of Polymyxin in Gram Negative Urinary Tract Infections. *J. Urol.* 66:564, 1949.
4. Kagan, B.M., et al.: Polymyxin B and Polymyxin E. *J. Lab. & Clin. Med.* 37:402, 1951.
5. Lieberman, D. and Jawetz, E.: Treatment of Chronic Shigella Infections in Children with Oral Polymyxins. *Pediatrics* 18:240, 1951.
6. Jawetz, E.: Infections with *Pseudomonas aeruginosa* Treated with Polymyxin B. *Arch. Int. Med.* 59:30, 1952.



BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe 7, N. Y.



## What does Enriched Bread give him Nutritionally?

CONSERVATIVE industry estimates indicate that the per capita consumption of bread in the United States is 5 ounces daily. Since the bulk of this output is enriched white bread, the amounts of essential nutrients supplied by this quantity become significant from a standpoint of national health.

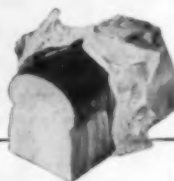
Contrary to widespread belief, enriched bread is considerably more than merely a source of caloric food energy. As the table indicates, 5 ounces of enriched bread supplies for a sedentary man, the following substantial proportions of his daily needs for these important nutrients: protein, 17%; thiamine, 28%; riboflavin, 12%; niacin, 26%; iron, 31%; calcium, 13%. Five ounces of bread also provides 16% of the daily caloric need.

This generous nutrient contribution is made at a cost of but a few cents, a fact which has led bread to be called a bargain in food.

Some twelve years ago, enriched bread came into widespread commercial production as a result of cooperation between industry and health authorities in the aim to improve the nutritional status of the American people. It has made a significant contribution to the improvement of national health and to the reduced incidence of severe and mild nutritional deficiency states.



The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.



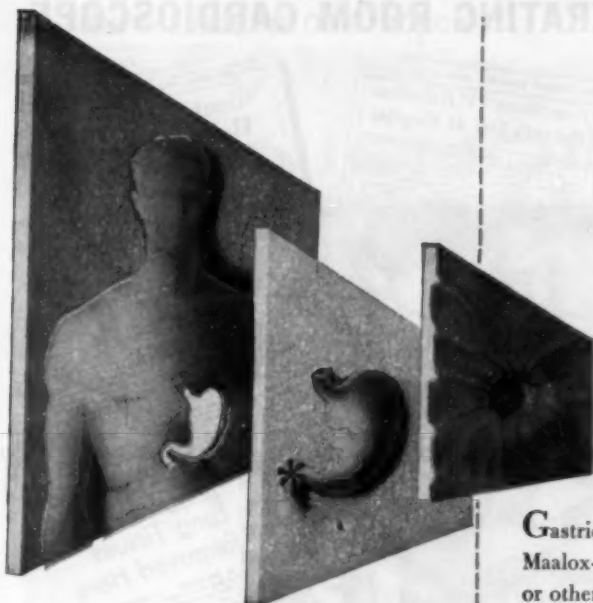
NUTRIENTS AND CALORIES CONTRIBUTED BY 5 OUNCES OF ENRICHED BREAD AND THEIR PERCENTAGES OF RECOMMENDED DAILY DIETARY ALLOWANCES\*

Nutrients and Calories	Protein	Thiamine	Riboflavin	Niacin	Iron	Calcium†	Calories
Amounts	12. Gm.	0.34 mg.	0.21 mg.	3.1 mg.	3.7 mg.	125 mg.	391
Percentages of Allowances	17%	28%	12%	26%	31%	13%	16%

\*Daily dietary allowances recommended by National Research Council for a sedentary man (154 lbs.)

†Estimated average

**AMERICAN BAKERS ASSOCIATION**  
20 NORTH WACKER DRIVE • CHICAGO 6, ILLINOIS



# maalox<sup>®</sup>

*gives ulcer relief*

*without side effects*

Gastric hyperacidity is controlled by Maalox-Rorer without constipation or other side effects commonly encountered with antacids. Relief of pain and epigastric distress is prompt and long-lasting. Available in tablets and liquid form.

Suspension Maalox-Rorer contains the hydroxides of Magnesium and Aluminum in colloidal form. The smooth texture and pleasant flavor make it highly acceptable, even with prolonged use.

**Supplied:** in 355 cc. (12 fluid ounce) bottles. Also in bottles of 100 tablets. (Each Maalox tablet is equivalent to 1 fluidram of Suspension Maalox.)

*Samples will be sent promptly on request.*

**WILLIAM H. RORER, INC.**

Drexel Bldg., Independence Square  
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## CAMBRIDGE OPERATING ROOM CARDIOSCOPE



## IN THE NEWS

This photograph and these news items are but a few of the many that have appeared in the public press since the introduction of the Cambridge Operating Room Cardioscope. The fact that this instrument has encouraged surgery on patients who are questionable risks because of heart condition, has captured the interest of the lay press as well as the attention of the entire medical profession.

The Cambridge Operating Room Cardioscope continuously shows the Anesthesiologist and Surgeon any lead of the patient's electrocardiogram and the instantaneous heart rate. Its sweep second hand is most convenient for timing respiration and for similar purposes. A cardiac standstill alarm gives audible warning instantly when the heart rate drops below a selected critical minimum.

The Cambridge "Simpli-Scribe" Direct Writing Electrocardiograph is a valuable adjunct to the Cardioscope. By simple operation of a remote control switch on the Cardioscope, any portion of

any lead of the electrocardiogram is instantly recorded upon the Direct Writer, which is located outside the operating room without attendance. In this manner, a continuous history of the patient's heart can be written during the entire operation.

The Cambridge Operating Room Cardioscope is explosion proof and may, therefore, be safely used within the operating room. The Electrocardiograph, however, should always be located outside the operating room where no explosive hazard exists.

The Cambridge Operating Room Cardioscope is a "must" for the modern hospital.

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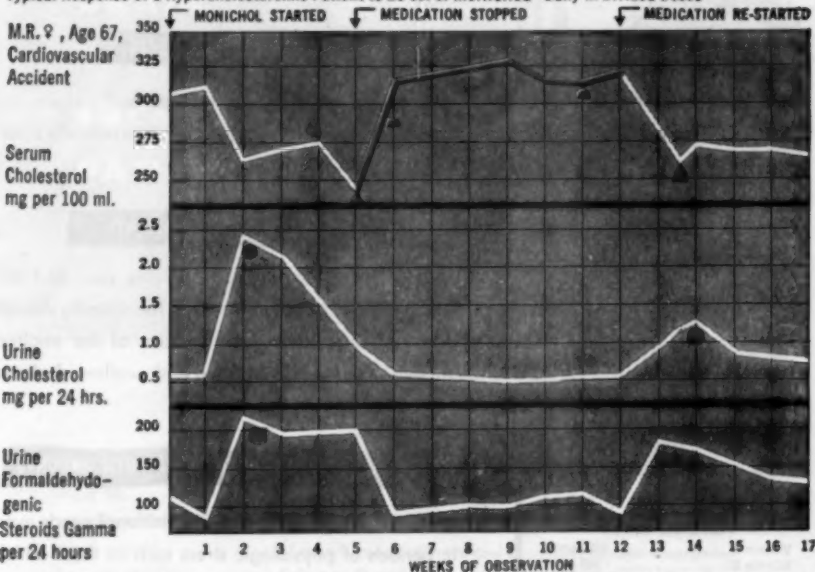
the realization of a hope...

... for a satisfactory preparation in the management of hypercholesteremia

# MONICHOL



Typical Response of a Hypercholesteremic Patient to 20 cc. of MONICHOL\* Daily in Divided Doses\*\*



The above graph demonstrates the effectiveness of MONICHOL in enhancing the stability of the serum lipid emulsion by: ▲ normalizing elevated serum cholesterol levels, ● changing the character of the excess serum cholesterol to facilitate urinary excretion, and ■ making the excess serum cholesterol more readily available for utilization by the adrenal cortex in steroid synthesis.\*\*

The sense of well-being experienced by patients on MONICHOL is attributed by the investigators\*\* to better utilization of excess serum cholesterol by the adrenal cortex. MONICHOL is entirely non-toxic.

The red portion of the graph shows that uninterrupted daily intake of MONICHOL is essential, because hypercholesteremia is probably due to an inborn error of metabolism.

Indications: For the therapeutic and prophylactic management of hypercholesteremia so frequently associated with cardiovascular disease and diabetes.

Formula: Each teaspoonful (5 cc.) contains: Polysorbate 80 500 mg. Choline Dihydrogen Citrate 500 mg. Inositol 250 mg. Minimum Dosage: Two teaspoonful twice daily after meals. Supplied: Bottles of 12 oz. Literature on request

\*\*Sherber, D. A., and Levites, M. M.: Hypercholesteremia. Effect on Cholesterol Metabolism of a Polysorbate 80-Choline-Inositol Complex (MONICHOL). J.A.M.A. 152:682 (June 20) 1953. \*Trademark

*Monichol normalizes cholesterol metabolism*

IVES-CAMERON COMPANY, INC., 22 East 40th Street, New York 16, N. Y.



# SUSTAGEN

a completely new approach to tube feeding



A 24 hour feeding of 900 Gm. supplies:

Calories.....	3500
Protein.....	210 Gm.
Fat.....	30 Gm.
Carbohydrate.....	600 Gm.

#### Vitamins and Minerals

Vitamin A.....	5000 units
Vitamin D.....	500 units
Ascorbic acid.....	300 mg.
Thiamine hydrochloride.....	10 mg.
Riboflavin.....	10 mg.
Niacinamide.....	100 mg.
Calcium pantothenate.....	40 mg.
Pyridoxine hydrochloride.....	5 mg.
Choline bitartrate.....	500 mg.
Folic acid.....	2.5 mg.
Vitamin B <sub>12</sub> (crystalline).....	4 mcg.
Iron.....	15 mg.
Calcium.....	6.3 Gm.
Phosphorus.....	4.5 Gm.
Sodium.....	1.9 Gm.
Potassium.....	7 Gm.

For detailed information, write for the booklet, "How to Use Sustagen."

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I. Abramson, Julia, Bresick, Elliot,  
and Sapient, P. L.  
*New England Jour. Med.*,  
243-44, July 12, 1950.

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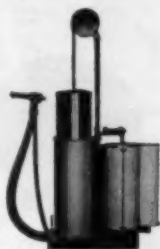
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1. Zelman, S.: Arch. Int. Med. 90:141, 1952.

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**REFERENCE:** 1. J. Pediat. 42:292 (March) 1953.

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# ANNALS OF INTERNAL MEDICINE

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## GIANT FOLLICLE HYPERPLASIA: A STUDY OF ITS INCIDENCE, HISTOPATHOLOGIC VARIABILITY, AND THE FREQUENCY OF SARCOMA AND SECONDARY HYPERSPLENIC COMPLICATIONS \*

By THEODORE S. EVANS, M.D., F.A.C.P., *New Haven, Connecticut*, and  
CHARLES A. DOAN, M.D., F.A.C.P., *Columbus, Ohio*

AN increasing number of patients with known chronic constitutional disease are being recognized in whom, during a period of satisfactory therapeutic control, either basic qualitative cellular alterations occur, or complicating secondary cytopenic episodes<sup>16</sup> develop, which are more immediately incapacitating and life-threatening than the primary dyscrasia itself. Under these circumstances, it is essential to reevaluate promptly the fundamental underlying pathologic-physiology. It has been found to be most important to differentiate monocytopenia and pancytopenia particularly carefully, as due either to central bone marrow invasion or damage, or to some *peripheral* mechanism—with special reference to one of the so-called secondary hypersplenic or dysplenic syndromes.

Among the more chronic types of lymphomata is one in which just such changes have been reported to occur not infrequently. "Giant lymph follicle hyperplasia" is a gross tissue, morphologic, descriptive term of the pathologists, still ill-defined because of the wide range of clinical syndromes with which it has been associated, without the establishment of a known etiologic factor. It has been variously interpreted relative to the morphologic specificity and functional potential of the cells making up the enlarged germinal

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From The Lymphoma Clinic, the Division of Research Hematology, Department of Medicine, Ohio State University, Columbus, Ohio, and The Yale University School of Medicine, and the Grace Unit of the Grace New Haven Hospital, New Haven, Connecticut.

Presented in part before the International Hematology Congress, Cambridge, England, August, 1950.

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centers, and both physicians and pathologists have been dependent, for the most part, on isolated observations in individual patients widely scattered as to time and place, so that the composite life history of this disease has been derived from fragmentary rather than from related and continuous data. Unlike others of the lymphomata, this particular gross pathologic picture has been described both as a localized and as a generalized phenomenon of the lymphatic tissues, occurring in both sexes and with similar relatively benign cytologic and clinical characteristics at any and all ages, from birth through the sixth decade.

Our attention has been focused in recent years on this architectural, morphologic entity from the two angles already mentioned: first, the differential diagnostic characteristics which distinguish this from the other lymphomata, as seen in the patients referred to our Lymphoma Clinic at the Ohio State University Health Center; and second, the high frequency of secondary hypersplenic cytopenic complications, which have been noted both here and in the Hematology Clinics at the Yale University Medical Center. For more than 10 years, both of these factors have been under intensive scrutiny in our clinics, during which period 1,617 patients have been diagnosed and treated by us for leukemia in Columbus, of which 831 were lymphatic in type. Since its establishment as a coöperating but independent research and therapy unit under the late Dr. Herman A. Hoster in 1942, approximately 300 patients have been followed in our Lymphoma Clinic, 13 of whom have been diagnosed as giant follicle hyperplasia, an incidence of 4.3 per cent, or 0.8 per cent of all lymphatic dyscrasias seen. To these are added three patients from the New Haven Clinics, to make a total of 16 patients presented in this communication, all of whom have been followed for a number of months or years. This provides the background of time and a large comparative clinical material, plus the facilities and the desire to evaluate critically every objective clinical manifestation and laboratory characteristic in each patient, without which the life histories of the lymphomata cannot hope ever to be distinguished or subjected to increasingly specific therapeutic management.

A review of the pertinent medical literature (see *Discussion*) tends to emphasize two significant characteristics of giant follicle lymphoma: (1) splenic involvement reportedly occurs early and commonly in this disease, and considerably more often than bone marrow invasion, and (2) a relatively chronic clinical course is the rule rather than the exception—a combination of circumstances which renders the patients with this disease peculiarly susceptible, we believe, to the development of secondary hypersplenic cytopenic episodes. In this series of 16 personally studied patients, the incidence of splenomegaly was 70 per cent—eight (or 50 per cent) requiring splenectomy for more or less acute cytopenic episodes. Three patients had acute hemolytic anemia as the predominating hematologic complication; two presented with thrombocytopenic purpura; one patient showed



both a profound neutropenic leukopenia and a thrombocytopenia; and the remaining two patients had a peripheral pancytopenia involving all of the circulating formed elements of the blood. Each of these syndromes was promptly reversed by the surgical removal of abnormal splenic tissue.

In one of the patients with panhematocytopenia undergoing successful splenectomy, the tissue pathology having shown giant follicular hyperplasia, there developed seven years later both the histocytologic and the clinical picture of lymphosarcoma, from the rapid general dissemination of which he quickly succumbed. Another of these patients currently shows suggestive evidence of reticulum cell sarcoma-metamorphosis, nine years postsplenectomy for giant follicle lymphoma, but has responded clinically to medical management during the 10 months since this apparent incipient change in underlying pathology was noted. The incidence of sarcoma findings, following the original biopsy diagnosis of giant follicle lymphoma in our 16 patients, is four (25 per cent).

Various hypotheses may be and have been advanced in explanation of these observations. The reason for our believing that *all* "giant follicles" are not composed of sarcoma lymphocytes, or that "lymphosarcoma" has not been coexistent within the giant follicles, either as a temporarily quiescent focus elsewhere than in the biopsied tissues, or as masked, unrecognized, "germinal center" cells, is that the clinical course of the disease, while under medical surveillance, has always changed so radically whenever the appearance of sarcoma elements has become unequivocal.

We believe the evidence justifies the tentative conclusion that giant follicle lymphoma, uncomplicated by the changes here cited, is a relatively chronic, readily controlled member of the lymphoma group of dyscrasias, and therefore justifies an optimistic though guarded prognosis to the patient; but at the same time to the attending physician must be emphasized his continuing responsibility for careful, regular, complete physical, hematologic and serial biopsy examinations in recognition of the possible complications which may, at times, condition the safety of his patient, either temporarily or basically. These opinions are supported by the following detailed analyses of the cases personally studied, together with a critical review of those heretofore reported in the medical literature.

#### CASE REPORTS

*Case 1. N. K. D.* An otherwise healthy girl between two and three years of age was first noted to pass some bright red blood in an otherwise normal stool. Physical examination revealed only an asymptomatic enlargement of the spleen. At four and one-half years of age her enlarged, infected tonsils were removed because of repeated throat infections, but unfortunately no histologic sections were made. Frequent febrile episodes recurred during the subsequent seven months, requiring repeated courses of chemotherapy. Splenomegaly continued to be a constant finding. No anorexia and no interference with normal growth and development were apparent to the attending pediatricians. Though no other gross hemorrhages recurred following the first reported bowel episode, the child was observed to bruise with increasing

case. One sibling and the parents enjoy normal health. No history of any familial blood or other dyscrasia has been elicited.

When referred, at five years of age, by Dr. H. F. Downing for further diagnostic studies because of the persistent splenomegaly, the child presented in June, 1948, with a temperature of 99.6° F., a pulse rate of 116 per minute, some pallor of the skin and mucous membranes, but no rash, petechiae or ecchymoses. Some moderate enlargement of the nodes in the posterior cervical chains existed bilaterally. Larger nodes were present in the left axilla. X-ray of the chest showed no mediastinal involvement. A soft systolic murmur could be heard over the entire precordium. Abdominal examination disclosed the firm sharp border of the spleen 4 cm. below the left costal margin, descending 2 cm. on deep inspiration. The liver was not enlarged.

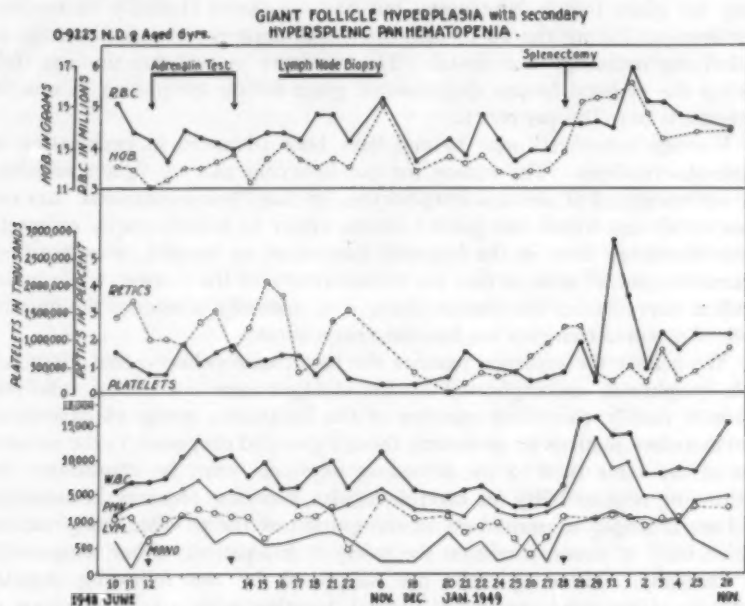


CHART I. Case I. N. D., F., aged 6 years. Giant follicle hyperplasia with secondary hypersplenic panhematopenia.

The blood findings were within normal limits; red blood cells, 4.0 million; hematocrit, 43 per cent; hemoglobin, 12.1 gm.; white blood cells, 5,150; platelets, 763,040 per cubic millimeter; sedimentation rate, 0.2 mm. per min. (normal). There were 2.8 per cent reticulocytes, however, and there was increased erythrocyte osmotic fragility (0.471 to 0.319 saline equivalent). Supravital study of the white cells revealed 37 per cent neutrophils, 27 per cent eosinophils, 24 per cent normal lymphocytes and 12 per cent normal monocytes. Examinations for trichinosis and intestinal parasites were negative; Wassermann, Kahn and agglutination tests for brucellosis, histoplasmosis, typhoid and paratyphoid fever were all negative. Renal and hepatic function tests, including routine blood chemical determinations, were all within physiologic limits.

Two successive bone marrow examinations failed to reveal any pathognomonic diagnostic cell data. There were 25 per cent small mature lymphocytes, not an unusual finding at this age, with active panhematopoiesis, but with no evidence of significant eosinophil or R-E cell hyperplasia. An "adrenalin test" revealed base line versus transitory maximal cell levels as follows: white blood cells, 6,550 to 13,000; red blood cells, 3.6 million to 4.5 million; hemoglobin, 11.0 to 12.0 gm.; platelets, 360,000 to 915,000 per cubic millimeter. These data were interpreted as indicative of pancellular splenic hypersequestration.

An enlarged left axillary lymph node was removed for histologic study. Both gross and microscopic evidence of giant lymph follicle hyperplasia was found without other pathognomonic cell changes. Prophylactic splenectomy was advised, but refused.

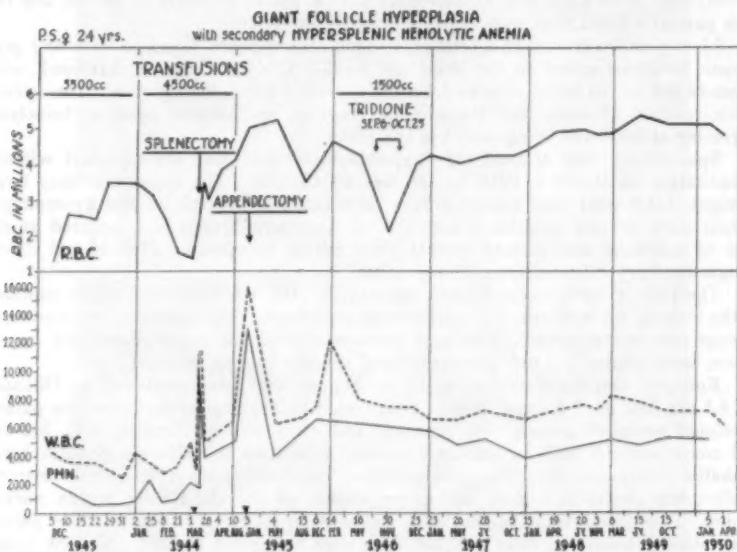


CHART II. Case 2. P. S., F., aged 24 years. Giant follicle hyperplasia with secondary hypersplenic hemolytic anemia.

During the next six months fluctuations in spleen size were noted, together with cytopenic changes in each of the circulating elements of the blood. A neutropenic leukopenia of 3,000 developed; the platelets fell to a low of 86,000; a refractory chronic low-grade anemia, hemolytic in type, persisted. The sternal bone marrow showed increasing hyperplasia of all normal elements, without maturation arrest or any toxic, infiltrative or leukemic abnormalities. All other laboratory data were within physiologic limits. The spleen was removed January 29, 1949, by Dr. Robert M. Zollinger during this subacute crisis (figures 7 and 8), and this was followed promptly by complete restoration of normal circulating blood levels (chart 1). There has been no evidence of further progression of the primary disease to date.

Case 2. P. S. A 24 year old female of Italian extraction was found in August, 1943, to have a positive Kahn but a negative Mazzini serologic test. Mitral stenosis with some enlargement of the heart was noted. The remainder of the physical and

laboratory examinations was within normal limits. Between September and November she received a series of injections of bismuth with Mapharsen, the last treatment being followed by nausea, vomiting, fever and retinal hemorrhages. She was admitted to the New Haven Hospital in December, 1943, for a persistent anemia. Physical findings of pallor, retinal hemorrhages, cardiac enlargement, splenomegaly and hepatomegaly led to a tentative diagnosis of rheumatic heart disease with suspected Mapharsen damage of the liver. The prothrombin, bromsulfalein and glucose tolerance liver function tests were normal, but the cephalin flocculation was positive 4 plus. The red cells varied between 1.2 million and 3.0 million (chart 2); reticulocytes, 3.5 per cent to 6.5 per cent; correspondingly low hemoglobin levels were recorded, with a neutropenic leukopenia and normal platelets. The bone marrow showed marked hyperplasia of the erythroid and myeloid series, with normal megakaryocytes. Both Kahn and Kolmer tests were negative on many occasions, and the male partner's blood tests were entirely negative for syphilis.

Liver extract, iron, and a total of 15 blood transfusions failed to have any permanent beneficial effect on the blood cell levels. Clinical jaundice developed, with a steady fall in red blood cells to 1.4 million, with 3.8 gm. hemoglobin. The icterus index reached 15 units and the osmotic fragility test became positive, hemolysis beginning at 0.050 and being complete at 0.030.

Splenectomy was advised for "hypersplenism" and was accomplished without complication on March 2, 1944, by Dr. Gervais Connor. The spleen was very large (weight, 1,000 gm.), and typical diffuse reticulum cell hyperplasia and hyperphagocytosis were present (figures 1 and 2). A mesenteric lymph node secured at the time of operation also showed typical giant follicle formation. Clinical and hematologic recovery followed splenectomy (chart 2).

The patient remained well until January 3, 1945, when she was again admitted to the hospital for a ruptured appendix with peritonitis. The appendix was removed; prompt recovery followed. The bone marrow showed the expected myeloid hyperplasia, with normal red cell generation and megakaryocytic function.

Epilepsy, first manifested clinically in August, 1945, was controlled by Dilantin, gr. 4.5 per day, until August, 1946. Transferred to Tridione at that time, the patient developed profound anemia with jaundice, and when seen in October, 1946, her red cell count was 2.0 million. On this hospital admission the albumin-globulin ratio, cephalin flocculation test, the icterus index, the bromsulfalein test, bone marrow studies, the electrocardiogram and x-ray studies of the chest were within normal limits. Two blood transfusions were followed by prompt recovery. The patient has remained hematologically well for more than nine years to date. No new lymph node enlargements have been identified despite repeated examinations. No evidence of progressive, giant follicle lymphoma has appeared during the past 10 years.

*Case 3. C. S.* A 47 year old white female was first seen in the New Haven Hospital in 1944. The surgical removal of localized enlarged left axillary lymph nodes established the histopathologic diagnosis of "typical giant follicle lymphoma." No other adenopathy or pathology was discovered at that time after complete x-ray and chemical laboratory studies.

The patient remained well until February, 1949, when pallor without jaundice or fever, weakness, vertigo and abdominal distress developed. There was no demonstrable regional adenopathy; both spleen and liver extended slightly below the respective costal margins. The red blood cell count was 2.0 million per cubic millimeter; hemoglobin, 7.5 gm.; the leukocytes were normal in number and quality. Sternal bone marrow studies revealed marked normoblastic hyperplasia without megakaryocytic or myeloid abnormalities. All other examinations were within normal limits. One blood transfusion was given at this time. The patient improved and was discharged from the hospital, but by April 6 all previously noted symptoms and

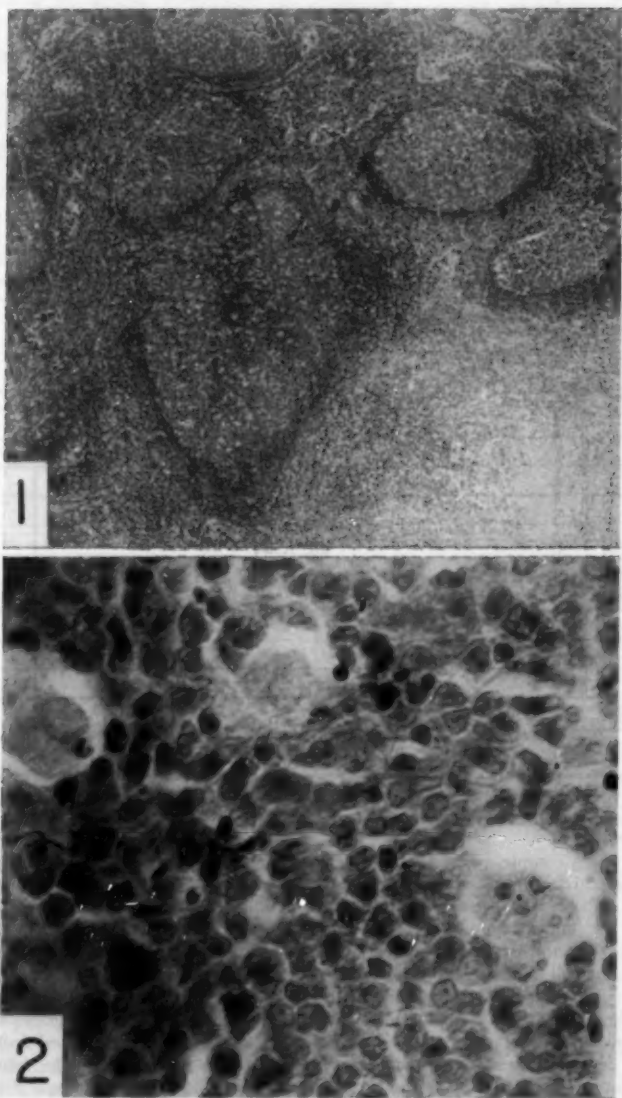


FIG. 1. *Case 2.* Mesenteric lymph node, showing multiple single and confluent follicles typical of spleen parenchyma and nodes at time of splenectomy.  $\times 50$ .

FIG. 2. *Case 2.* Splenic parenchyma with diffuse R-E cell hyperplasia, involving also the follicular germinal centers. Active phagocytosis is observed in those large R-E cells in direct contact with the tightly packed foci of red cells.  $\times 1100$ .





correction of an earlier postpoliomyelitic paralysis. Though no abnormal bleeding tendencies, spontaneous or postsurgical, were observed at that time, the history recorded a statement that the patient had "always bruised easily." Except for a single attack of chorea, this patient remained well until June, 1945, when at age 15 years she reappeared with the chief complaint of increasingly prolonged and profuse menstrual bleeding. Two weeks previously skin petechiae and ecchymoses had developed, and three days before admission she had noted sudden marked weakness, diaphoresis and pallor. Physical examination at this time revealed an obese, well developed, extremely pallid girl. Small petechial hemorrhages covered the skin and mucous

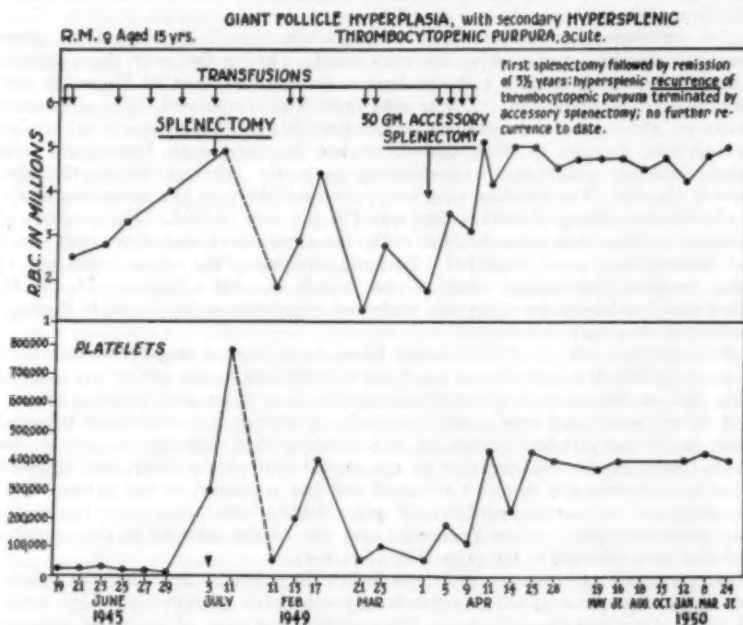


CHART IV. Case 4. R. M., F., aged 15 years. Giant follicle hyperplasia with secondary hypersplenic thrombocytopenic purpura, acute. A recurrence 3 years and 8 months later was promptly and completely relieved by accessory splenectomy.

membranes, and large ecchymoses were present on all four extremities. The Rumpel-Leede test was strongly positive. The heart rate was rapid and there was a soft systolic murmur. The spleen, liver and lymph nodes were not remarkable, and no other significant physical abnormalities were recorded.

The family history revealed on this admission the interesting fact that two cousins had died of "leukemia with purpuric manifestations."

Initial blood studies confirmed the peripheral thrombocytopenic basis for the clinical purpura without significant qualitative alterations in the other elements (chart 4), and bone marrow examination established the fact of megakaryocytic hyperplasia, without medullary necrosis or aplasia or leukemic abnormalities, which strongly suggested a hypersplenic mechanism. The bleeding time was prolonged,

the coagulation time normal. Additional pertinent laboratory data established the fact that all other organic functions were normal.

A diagnosis of primary thrombocytopenic purpura hemorrhagica (hypersplenic type) was made, splenectomy advised, and a moderately enlarged spleen weighing 150 gm. was removed without complication July 3, 1945. A single accessory spleen 1 cm. in diameter was removed within the pedicle of the enlarged mother spleen. The platelets rose promptly in the circulation, and all hemorrhagic manifestations ceased at once. Microscopic examination of these tissues revealed "giant lymph follicle hyperplasia" as the primary abnormality with reticulum cell hyperplasia, and hyperphagocytosis of histologically interpreted platelets sequestered in the splenic parenchyma.

The remission was complete and was maintained until October, 1948, when generalized petechiae and ecchymoses reappeared. During the next three months the menses became gradually more prolonged and profuse, and in December two severe epistaxes occurred and a state of mild shock was precipitated. The circulating platelets on admission were found to be less than 10,000, though supravital studies of living bone marrow elements showed marked megakaryocytic hyperplasia with platelet-producing cytoplasmic fragmentation, as in the previous similar thrombocytopenic episode. The bleeding time was prolonged, with no clot retraction at the end of 48 hours; the prothrombin time was 100 per cent normal. The presence of an accessory spleen was suspected, but conservative measures, including fresh whole blood transfusions, were employed. Purpuric symptoms and signs continued to require frequent transfusions until, on the fourth hospital admission, March 31, another complete laboratory study was made and reexploration was urged in the hope of finding an accessory spleen.

Preceded by 1,500 c.c. of fresh whole blood, an abdominal surgical reexploration was made by Dr. Malcolm Allison on April 4, 1949, and at the site of the original pedicle ligation an accessory spleen measuring 6 by 5 by 4 cm. and weighing an estimated 50 gm. was found and readily removed. A prompt rise once again occurred in the circulating platelets (chart 4), the bleeding time returned to normal, the Rumpel-Leede test became negative on the second postoperative day, and complete clinical and hematologic recovery followed and has continued to the present time. Both gross and microscopic evidences of giant follicle hyperplasia were recognized in the accessory splenic tissue (figure 3) and also in the sections of the appendix which had been removed at the same time (figure 4).

*Interpretation:* Chronic giant lymph follicle hyperplasia, involving the spleen; acute thrombocytopenic episode, terminated by successful splenectomy. This remission lasted three and one-half years, followed by recurrence of a similar subacute clinical and hematologic picture which continued for six months, requiring repeated fresh whole blood replacement transfusions. Reexploration was finally advised and a 50 gm. accessory spleen was removed from a site near the original pedicle, where a single small accessory spleen had been seen and removed at the first operation. This second splenule, previously inconspicuous and overlooked at the first surgical operation, must have hypertrophied to its ultimate size during the intervening three year period and have become increasingly pathologic for the circulating thrombocytes during the six months of purpuric signs which led to the second surgical exploration. Both grossly and histopathologically, this secondary satellite spleen was a replica of the original mother spleen. The patient has remained entirely well now for approximately five years.

*Case 5. R. L. B.* A male, age 47 years, was first seen by one of us July 5, 1950, with the chief complaint of fever, chills, low back pain and an enlarged, painful mass in the right inguinal region, with edema of the right leg and ankle. In 1943 the patient had first noted a localized enlargement of the nodes at the angle of the

jaw and in the cervical chain in the left neck. A surgical lymph node biopsy was performed and the diagnosis of "giant follicular lymphoma" was made by Dr. Joseph Hill, clinical pathologist at Baylor Hospital, Dallas, Texas (personal communication). Deep x-ray therapy was followed by the disappearance of all swelling. A recurrence in 1944 was again successfully treated by x-ray therapy. In 1946, enlarged nodes developed in the inguinal region and a series of local x-ray treatments again reduced this swelling.

No further symptoms or signs were noted until February, 1950, when swelling and tenderness of the right cervical and of the left axillary nodes were noted, and chills and fever to 104° F. developed. A chest x-ray at this time revealed enlargement of the mediastinal nodes. A second lymph node biopsy was performed and the original diagnosis was again confirmed by the pathologist, Dr. Joseph Hill. A series of eight x-ray treatments was received, followed by one administration of radioactive phosphorus. All symptoms and signs regressed and the patient felt reasonably well until 10 days prior to admission to the University Hospital, when fever, low back pain and right inguinal adenopathy developed during a visit to Ohio.

On physical examination the temperature was 99.8° F.; pulse, 88; blood pressure, 120/78 mm. of Hg. Skin and mucous membranes were pale; no petechiae or ecchymoses were seen; the conjunctivae were injected. Scars in both right and left cervical regions marked the previous biopsy sites. Only in the right inguinal region were large and tender nodes found. The mediastinum was clear to physical and x-ray examinations. The spleen was palpable 1 cm. below the left costal margin on deep inspiration, and percussion dullness extended upward 2.5 cm. in the anterior axillary line. The liver was not appreciably enlarged and no masses were palpable within the abdomen. The right ankle and foot showed moderate pitting edema.

The initial hematologic data were as follows: total white blood cells, 3,850; red blood cells, 3.2 million; platelets, 39,000 (normal, 750,000); reticulocytes, 2.2 per cent; supravital differential of the white blood cells: neutrophils, 88 per cent; eosinophils, 3 per cent; small lymphocytes, 7 per cent; monocytes, 2 per cent. Sternal marrow aspiration revealed pancellular hyperplasia of all normal blood elements without maturation arrest, toxic depression or foreign cell infiltration. A moderate left shift to late erythroblast and myelocyte "B" stages reflected qualitatively the increased quantitative activity of the marrow, and the increase in intermediate and young mononuclear megakaryocytes was interpreted to indicate their compensatory response to an excessive peripheral demand for platelets. No reticulum cell hyperplasia, as such, was observed. An adrenalin test revealed the following data: at basal conditions, baseline average: white blood cells, 3,800; red blood cells, 3.2 million; platelets, 39,000 per cubic millimeter; 20 minutes post-adrenalin maximal cellular peaks: white blood cells, 9,550; red blood cells, 3.4 million; platelets, 299,200. Splenectomy was recommended and the patient was returned to Dr. Hill at Dallas, Texas, for further study. The spleen was successfully removed by Dr. Farland Rushing, of Longview, Texas. The hematologic and clinical response was immediate.

Sections of the spleen showed focal areas of hyperphagocytic reticuloendothelial cell hyperplasia and evidence of parenchymal blood cell hypersequestration confirmatory of the earlier bone marrow and adrenalin studies.

Our own blood studies, made three weeks postoperatively in Columbus, Ohio, gave the following data: total white blood cells, 20,000 to 25,000; total red blood cells, 5.3 million; hemoglobin, 13.0 gm.; hematocrit, 45 per cent; platelets, 1,849,000; reticulocytes, 2.4 per cent; supravital differential: polymorphonuclears, 74 per cent; eosinophils, 6 per cent; normal small lymphocytes, 18 per cent; monocytes, 2 per cent.

The clinical course, however, seemed to have changed suddenly from a very chronic, easily controlled syndrome to a progressive febrile fulminating disease with generalized hypertrophy of all lymphatic tissues, resistant to x-ray and to all other

therapeutic controls. A lymph node biopsy at this time showed a histopathologic architecture and cellularity more compatible with lymphosarcoma than with the original picture of giant follicle lymphoma. The transition from "benign giant follicle lymphoma" to other, more malignant cellular states, such as lymphosarcoma, has been described, and "it is probable that this patient exemplifies such a cytologic

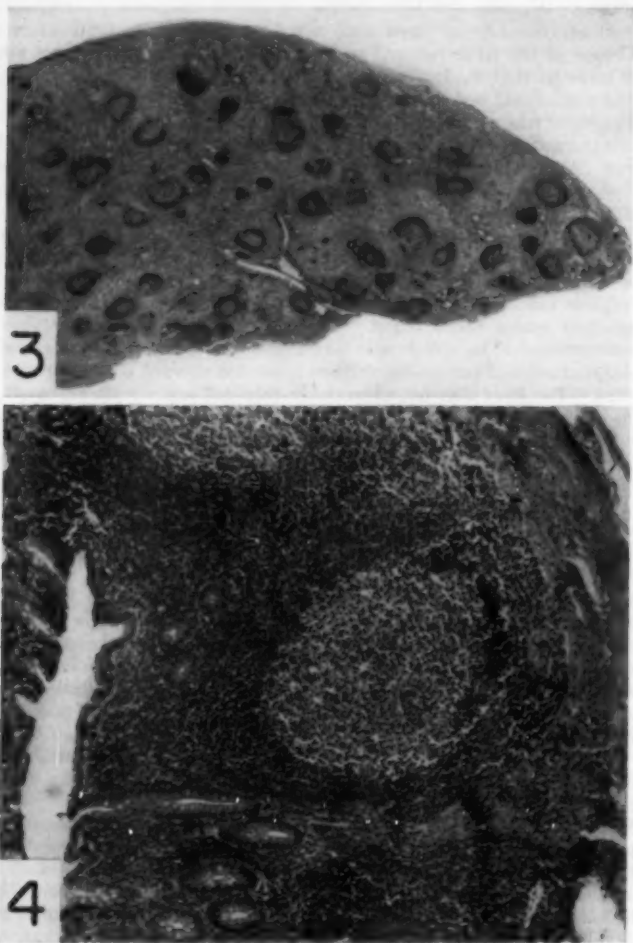


FIG. 3. Case 4. Accessory spleen (weight, 50 gm.), showing multiple giant follicles similar to those seen in the original mother spleen removed four years earlier for thrombocytopenic purpura. The recurrent syndrome was promptly and permanently corrected by the second accessory splenectomy.  $\times 10$ .

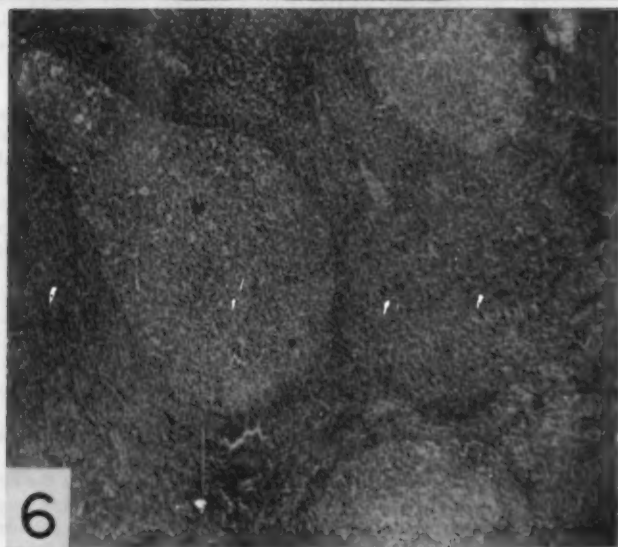
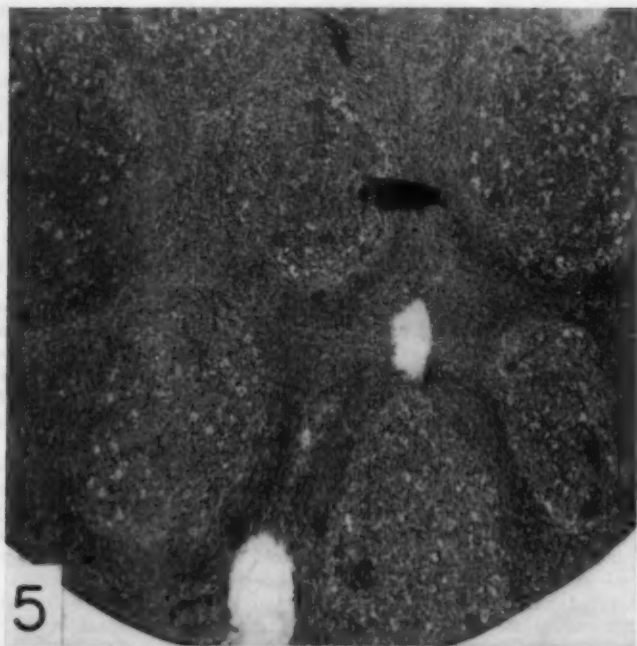
FIG. 4. Case 4. Many lymph follicles with markedly enlarged germinal centers were found in the appendix removed at the time of the accessory splenectomy.  $\times 50$ .

and clinical metamorphosis." While the splenectomy permanently controlled the peripheral pancytopenia, with its attendant dangers, it did not prevent the progressive spread of the sarcoma, with an ultimately fatal outcome several months later.

*Case 6. A. C. K.* This white female has been under continuous medical observation since birth in the spring of 1947. When she was four months of age, splenectomy was successfully accomplished for a severe type of hemolytic anemia, thought at that time to be congenital hemolytic jaundice. Recovery from the clinical icterus and associated anemia followed the surgery and was maintained for approximately one year. Intermittent episodes of severe anemia then recurred, necessitating supplemental transfusions of whole blood. Because of the similarity of the clinical and hematologic pictures to the original syndrome, surgical reexploration was undertaken in the summer of 1950 in a search for an accessory spleen, but without positive findings and with no tissue biopsies.

In November, 1952, this patient was referred by Dr. Marion Beard, of Louisville, Kentucky, and was admitted to University Hospital for further differential diagnostic studies. The chief complaint was chronic anemia, resistant to folic acid, iron, liver extract, vitamin B<sub>12</sub>, cortisone and multi-vitamin supplements, and having required repeated blood transfusions at frequent intervals since the latter part of 1948. The child had been otherwise asymptomatic, with normal gains in height and weight and with no apparent mental or physical retardation or defects (walking at 14 months and talking at 18 months of age). Measles in 1951 and infectious mononucleosis in February, 1952, without complications or sequelae, have been the only specific illnesses. There is no family history of hemolytic anemia or any other blood dyscrasia in either parent or the grandparents, and appropriate objective blood tests in these relatives and in the two normal healthy siblings have failed to reveal any of the stigmata of congenital hemolytic icterus. The positive physical findings in this patient included enlarged cryptic tonsils, bilateral; shotlike cervical nodes; grade III systolic murmur in the left fourth intercostal space at the sternal border without cardiac enlargement; palpable left lobe of the liver, with right hepatic border of dullness extending 3 cm. below the right costal border, and moderate keloid scar tissue reaction at the site of the previous surgical incision. Pallor—but no clinical icterus, and no petechiae or ecchymoses—was evident in a careful survey of skin and mucous membranes.

The initial laboratory survey revealed: Rh factor, positive; white blood cells, 18,000, with 38 per cent normal mature neutrophilic granulocytes, 9 per cent eosinophils, 1 per cent basophils, 1 per cent metamyelocytes, 39 per cent normal mature small lymphocytes, and 12 per cent normal mature monocytes; red blood cells, 3,320,000; hemoglobin, 11.3 gm.; reticulocytes, 2.0 per cent; hematocrit, 36 per cent; M.C.V., 109 cubic microns; M.C.H., 34 micromicrograms; M.C.H.C., 31 per cent; erythrocyte sedimentation index, 0.4 mm. per minute; blood platelets, 1,248,000 per cubic millimeter. A careful search of the supravital stained blood films failed to reveal any qualitative abnormalities suggestive of leukemic or sarcoma changes in the white blood cells. In addition to the absence of spherocytes and microcytosis in the red blood cells, the lack of any reticulocytosis was particularly significant. The warm hemagglutinin studies were also negative, using the Coombs' anti-globulin serum, the albumin technic and the trypsinized red cell tests. Cold agglutinins were also within the normal range in all tests, using both albumin and trypsin technics. The osmotic fragility studies, both before and after incubation, produced symmetrical curves of a lesser slope than normal: the bottom part of the curves at 0.6 per cent NaCl equivalent demonstrated some increased hemolysis; the middle of the curves was within normal limits; the top portion of the curves (to 0.1 per cent NaCl equivalent) showed decreased hemolysis, being atypical for any of the usually recognized hemolytic mechanisms. The mechanical erythrocyte fragility before incubation was 10.8



FIGS. 5-6.



(normal range, 1 to 7); after incubation, 24.1 (normal range 8 to 14). Multiple studies of the bone marrow from various sites showed a uniform cellular hyperplasia involving principally the erythroid elements at the normoblastic level, without evidence of maturation arrest or any toxic characteristics or cellular debris; myelopoiesis and megakaryocytosis were well within physiologic limits; the clasmatoocytes were normal in number, distribution and phagocytic activity; there was no infiltration of lymphocytes, monocytes or plasma cells, no reticulum cell hyperplasia, and no foreign cell invasion.

Urinalyses were repeatedly normal with evidence of good renal concentrating capacity; blood urea nitrogen, 14 mg. per cent; total plasma proteins, 6.8 per cent; albumin, 4.0 per cent; globulin, 2.8 per cent; prothrombin, 70 per cent; cephalin flocculation, negative; thymol turbidity, 5 per cent; van den Bergh: direct, 0.6 per cent; indirect, 1.7 per cent (recheck confirmed); blood sugar, 177 mg. per cent (recheck, normal range); serum sodium, 145; potassium, 5.7; chlorides, 108. Heterophil agglutination, normal range.

An attempt to localize hyperphagocytizing cells by Thorotrast visualization was determined upon because: (1) a clinical and hematologic retest confirmed cortisone failure to improve the erythrolytopoietic disequilibrium in this patient; (2) there was obvious normoblastic hyperplasia of the bone marrow, in an apparently current unsuccessful attempt to overcome the persistent peripheral anemia, though splenectomy had afforded a 12 month remission earlier; and (3) surgical reexploration had failed to discover the suspected accessory splenic tissue as the continuing cause of this anemic syndrome. Following initial scout films of the abdomen, three intravenous injections of 25 mg. each of Thorotrast were given at 24 hour intervals, and stereoscopic x-ray plates of the hepatosplenic areas were obtained. The radiologist's interpretations: "These comparable films show a fairly definite accessory nodule in the left anterior oblique view, lying beneath the stomach—apparently an accessory spleen."

After all of the evidence was reviewed once again, a third abdominal exploration was decided upon in an attempt to find further concealed splenic satellites responsible for the recurrent hemolytic crises, or, failing that, to secure histologic evidence of some other responsible pathologic process. Dr. Edwin Ellsion undertook this assignment on December 10, 1952, with the following report: "Despite complete mobilization of the entire left upper quadrant, and careful inspection and palpation of all of the sites where accessory spleens occur, we failed to find the splenic tissue which the x-ray films suggested. There were, however, numerous large suprapancreatic lymph nodes, and it is possible that these may represent what was visualized in the x-ray plates. There were also numerous mesenteric nodes. Perhaps from the following surgical biopsied specimens may be obtained some information which will be of help: (1) suprapancreatic lymph nodes, (2) lymph nodes at ileocaecal valve, (3) mesenteric lymph nodes, (4) appendix, (5) two samples of liver." Microscopic study of the sections from the several lymph nodes showed "uniform enlargement of the lymph follicles with prominent germinal centers showing reticulum cell hyperplasia without other architectural or cellular changes of diagnostic significance." Particularly prominent were the large confluent follicles with increased germinal centers in the walls of the appendix. The liver sections showed "slight fibrosis and appreciable amount of intracellular brown pigment deposition." The marked in-

FIG. 5. Case 6. Both spleen and mesenteric lymph nodes showed giant follicular hyperplasia, as illustrated in this low power photograph. The large scattered R-E cells within the germinal centers may be seen on close inspection.  $\times 50$ .

FIG. 6. Case 7. The greatly enlarged germinal centers common to both spleen and mesenteric nodes here show diffuse R-E cell hyperplasia with active intracellular phagocytosis. No evidence of irreversible progress of this cytologic process followed the removal of these tissues over an 8 year period; the leukothrombopenia has been permanently corrected to date.  $\times 50$ .

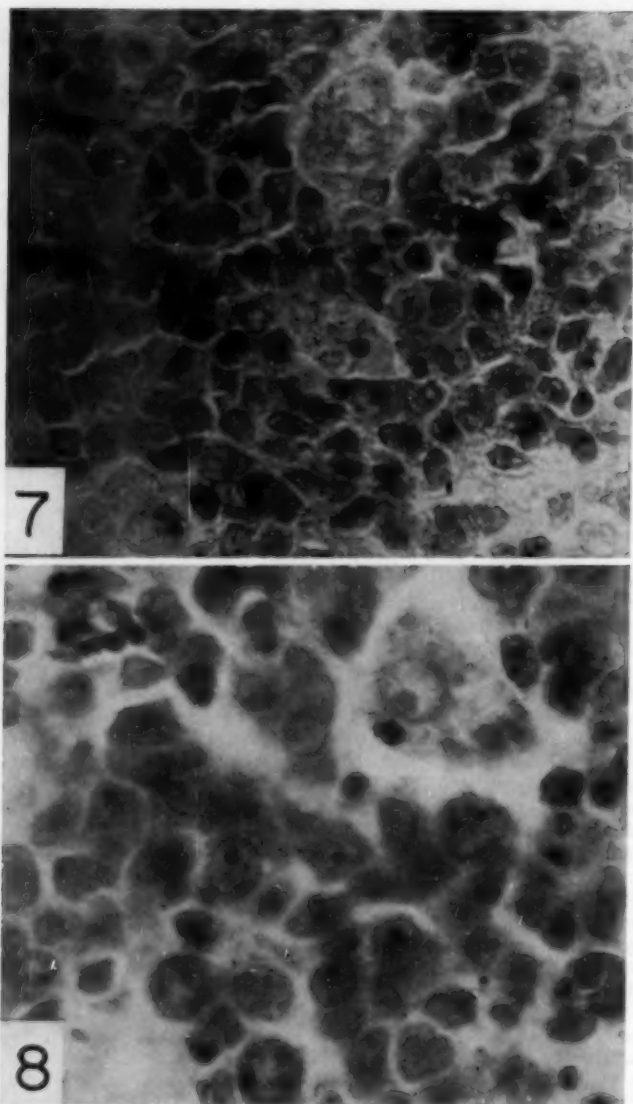


FIG. 7. *Case 1.* Cellular detail in the follicular germinal center. Note particularly the multiple nuclear mitoses in the smaller R-E cells in this field, as well as the enlarged R-E phagocytes similar to those seen in figure 2.  $\times 1100$ .

FIG. 8. *Case 1.* Note here the vesicular nuclear detail, with prominent nucleoli characteristic of the predominating reticulum cells in this field, in addition to the active cellular phagocytosis, which has occurred in the very large R-E cell.  $\times 1100$ .

crease in reticulum cell hyperplasia and phagocytic clasmotocytosis, with evidence of increased red cell ingestion in lymph nodes, would seem to be the most probable basis for the localized Thorotrast opacity seen in the x-ray films.

The findings led to speculation regarding the histopathology of the original splenic tissue removed from this little patient at four months. Was the splenomegaly at that time the first manifestation of "giant follicle lymphoma," and therefore responsible for the secondary hypersplenic hemolytic anemia crises? Fortunately, sections from the surgical spleen were available for further microscopic study and comparison, and the judgment of independent pathologists confirms the identity of the pathologic picture then and now (figure 5).

It will be remembered that "large cryptic tonsils" were among the positive physical findings in this young patient on the first admission to University Hospital. The isolation of hemolytic streptococci from these crypts and recurrent throat infections led to a desire on the part of both parents and physicians to eliminate these foci of infection. On March 25, 1953, the patient was readmitted to the University Hospital and a complete tonsillectomy and adenoidectomy were successfully accomplished, without complications. All removed tissues were subjected to microscopic study. Once again, the histopathologic picture was identical with all previous similar tissue studies: "Giant lymph follicle hyperplasia without structural or architectural nodal breakdown."

Since a fairly generalized lymphadenopathy of giant lymph follicle histopathology had been confirmed without direct or indirect evidence as yet of bone marrow invasion, and since the reticulocytes rose following the last abdominal surgical exploration to a high of 13.8 per cent, without any appreciable change in the red cells, small doses of radioactive phosphorus and cortisone have been started in an attempt to reduce the generalized reticulum cell and germinal center hyperplasia, and thereby the continuing "hemolytic" anemia. The Coombs' tests continue to be negative.

Clinically, the patient is reported by her parents to be much more active, to be more resistant to upper respiratory infections, and to have gained six pounds in weight. To date there is no evidence pointing toward Hodgkin's granuloma, lymphosarcoma or lymphatic leukemia, and we are hoping for a continuing benign course. The most recent hematologic picture (1954) is as follows: total white blood cells, 7,700; total red blood cells, 3,200,000; hemoglobin, 10.5 gm.; reticulocytes, 1.6 per cent; blood platelets, 666,400 per cubic millimeter. Supravital differential showed polymorphonuclears, 62 per cent; eosinophils, 2 per cent; normal small lymphocytes, 27 per cent; and monocytes, 8 per cent. Present diagnosis: congenital giant follicle lymphoma; duration: birth to present (six years of age).

*Case 7. J. T.* A 32 year old male was referred to one of us for differential diagnosis and treatment by Dr. E. R. Musick, of Oklahoma City, in June, 1944. The chief present complaints were those associated with the leukopenia and thrombocytopenia which had been found in routine laboratory studies. A Banti's syndrome had been suspected. Complete laboratory studies in the University Hospital served to focus attention upon the marrow-spleen mechanism rather than on hepatosplenic syndrome. All liver function tests were within physiologic limits. A representative peripheral blood study showed: total white blood cells, 3,300; total red blood cells, 4,610,000; hemoglobin, 12.2 gm.; reticulocytes, 0.8 per cent; blood platelets, 481,280 per cubic millimeter. Repeated marrow examinations confirmed a normal compensatory myeloid and megakaryocytic hyperplasia with adequate erythropoiesis. The presence of increased numbers of reticulum cells, however, pointed either toward a Hodgkin's syndrome or other similar primary R-E cell histopathologic disturbance, suggesting that the hypersplenic cytopenia was of the secondary type. Splenectomy was nevertheless advised and accepted. The splenic histopathology confirmed the R-E cell hyperplasia of the marrow. The prognosis was guarded. A prompt re-

versal of the peripheral blood picture followed, with amelioration of all symptoms, and the patient was not seen again until October, 1952, having remained in good health with no further therapy throughout the intervening eight years.

During the two years preceding his return, enlargement of the axillary lymph nodes had been noticed, and a very gradual weight loss of 15 pounds had occurred during the last 12 months. He remained otherwise asymptomatic. The peripheral blood studies were not diagnostic, so that an axillary lymph node was removed for microscopic study. The germinal centers showed unusually large giant follicular structure, with the remaining architecture of the node within normal physiologic limits. There were large reticulum cells, with moderately large individual nucleoli scattered throughout these germinal centers. No typical Sternberg-Reed cells were encountered, and neither the eosinophilia nor the neutrophilia of a granuloma was present. Our interpretation, concurred in by the members of the Department of Pathology, was "giant follicular blastoma with questionable early reticulum cell sarcoma changes." The picture was essentially that seen in the spleen eight years earlier. Radioactive phosphorus therapy was advised, and 3.5 mc. were given before the patient was discharged from the hospital with advice to watch carefully for any signs of further extension of the adenopathy. During the following 10 months, and without any additional therapy, there have been no clinical or hematologic signs of further progression, which tends to confirm a continuing, relatively benign, giant follicle lymphoma, rather than the reticulum cell sarcoma metamorphosis which was suggested in October, 1952.

*Case 8. K. L.* A female, age three years, was referred by Dr. W. F. Schmiesing for differential diagnosis and was admitted to the University Hospital April 8, 1953. Signs of easy bruising had been present for two months, with spontaneous petechiae and ecchymoses first appearing on the abdomen and torso, later on the buttocks and extremities. A persistent hematoma of the right index finger and recent epistaxis completed the history of the present illness. There was no family history of any bleeding or other hematologic dyscrasias, and the past medical history of the child included a normal term delivery following an uncomplicated pregnancy with physiologic developmental history. No allergic manifestations have ever been evident in patient or relatives.

Except for the evidence of generalized purpura over the entire body there were no other significant physical findings. Temperature, pulse and respirations were normal and compatible with the absence of any limitation of the observed physical energy and activity on the part of the patient. There was no regional adenopathy and no evidence of splenic or hepatic enlargement or other intra-abdominal or intra-thoracic pathology. The hematologic data were as follows: white blood cells, 11,200; red blood cells, 4,200,000; hemoglobin, 10.9 gm.; reticulocytes, 3.0 per cent; blood platelets, 16,000 per cubic millimeter; supravital differential white count: neutrophilic granulocytes, 38 per cent; eosinophils, 17 per cent; normal lymphocytes, 40 per cent; normal monocytes, 5 per cent. Sternal marrow aspiration showed physiologic erythromyelopoiesis, with a marked relative and absolute increase in megakaryocytes of varying size and age range. There were no toxic abnormalities, no foreign cell invasion, no reticulum cell hyperplasia, no leukemic changes.

*Interpretation:* Compensatory megakaryocytosis, secondary to primary hypersplenic thrombocytopenic purpura. All other pertinent laboratory data being negative, immediate fresh whole blood transfusions to be followed by splenectomy were advised. A 56 gm. spleen was removed without complications by Dr. Berlin, of Lima, Ohio, and the following report of the splenic histopathology was made by Dr. C. L. Blumstein, pathologist, Mercy Hospital, Coldwater, Ohio: "Multiple sections of splenic tissue reveal an increased number of lymphoid follicles with marked germinal follicular hyperplasia showing definite reticulum cell increase and surrounded by a rim of small

lymphocytes. The surrounding pulp shows empty sinuses with occasional immature large megakaryocytes, and a moderate number of eosinophils. This does not appear to be diagnostic of Werlhof's disease. Diagnosis: Hyperplasia of lymphoid germinal follicles of the splenic tissues." These sections were subsequently made available for personal study, and the foregoing interpretation was fully confirmed by the authors and by the personnel in the Department of Pathology, Ohio State University.

The immediate presurgical hematologic study revealed "no platelets" in the circulating blood, with the other data as already presented. Twelve hours postsplenectomy, the blood platelets were 492,000 per cubic millimeter; white blood cells, 30,000, with 92 per cent neutrophilic granulocytes, 8 per cent lymphocytes; red blood cells, 3,900,000; hemoglobin, 11.0 gm. With ligation of the splenic pedicle there was immediate cessation of oozing of the nonclotting blood in the operative field, with normal clot formation thereafter. "She was discharged from the hospital on the fifth post-operative day, and all residua of the purpura had practically disappeared, the general condition of the child was excellent," and has continued to remain so during the intervening six months. It remains to be seen whether the primary splenic "giant follicle lymphoma" in this young child, which precipitated an acute thrombocytopenic purpuric crisis requiring emergency splenectomy, will subsequently become evident in other lymphatic tissues, as happened in case 6. The prognosis we believe to be guardedly optimistic.

#### CONTROL SERIES WITHOUT HYPERSPLENIC CYTOPENIC SYNDROMES

During the period of years in which the foregoing eight cases with hypersplenic crises have been seen and followed, there have been discovered and treated in the Lymphoma Clinic at Ohio State University \* eight additional patients in whom a diagnosis of giant follicle lymphoma was established by tissue biopsy (table 1) without this complication. The age at onset of symptoms or signs ranged from 11 to 67 years; there were three females, five males. One woman patient continues in good health 14 years after the first signs of lymphoma were manifest at 38 years of age, and another (J. L.) continues without signs or symptoms after five years. Three others have continued under observation and treatment from 18 months to four years without any evidence of change from a relatively benign lymph follicle hyperplasia.

However, in one 38 year old male (B. P.) during a five year period of observation, the histopathologic picture changed definitely from that of a benign giant follicle lymphoma to that of lymphosarcoma with splenomegaly. The ensuing anemia was myelophthisic in origin, however, and a fatal termination came quickly after the second diagnostic biopsy, despite intensive treatment for the sarcoma.

Between July, 1949, and April 1950, C. O., a 50 year old male, after a four year history with the more benign histopathologic picture of giant follicle lymphoma, developed the cellular characteristics of lymphosarcoma with splenomegaly. The ultimate outcome in this patient is not known.

In February, 1952, H. H. K., age 62 years, presented with anemia and splenomegaly, and a lymph node biopsy showed both giant lymphoma

\* These data were summarized by Dr. John W. DeVore, who succeeded Dr. Herman A. Hoster as Medical Director of the Ohio State University Lymphoma Clinic.

TABLE I  
Giant Follicle Lymphoma, with Hypersplenic Syndrome

Case	Patient	Sex	Age	First Evidence of Disease	Duration of Symptoms	Diagnosis	Splenomegaly	Hematology	Splenectomy	Other Rx for Lymphoma	Present Condition
I	N. K. D.	F	2 yrs.	1943	9 yrs.	Ly. n. biopsy 6/48	Yes	Panhematopenia	Yes	None	Good
II	P. S.	F	24 yrs.	1943	10 yrs.	Ly. n. and spleen 3/44	Yes	Hemolytic anemia	Yes	None	Good
III	C. S.	F	47 yrs.	1944	9 yrs.	Ly. n. biopsy '44	Yes	Hemolytic icterus	Yes	None	Good
IV	R. M.	F	10 yrs.		8-13 yrs.	Ly. n. and spleen 7/45	Yes	Thrombocytopenic purpura	Yes	Accessory spl. removed '49	Good
V	R. L. B.	M	47 yrs.	1943	10 yrs.	Ly. n. biopsy '43 and '50	Yes	Panhematopenia	Yes	HN <sub>2</sub> Aminopterin P <sub>32</sub>	Dec'd Ly. sarcoma Good
VI	A. C. K.	F	Birth	1947 at birth	6 yrs.	Spleen at 4 mo.	Yes	Hemolytic anemia	Yes	P <sub>32</sub>	Good (? early retic. cell sarcoma changes)
VII	J. T.	M	41 yrs.	1944	9 yrs.	Spleen 6/44	Yes	Leukopenia and thrombocytopenia	Yes		Excellent
VIII	K. L.	F	3 yrs.	4/53	6 mos.	Spleen 4/53	Yes	Thrombocytopenic purpura	Yes	None	

Giant Follicle Lymphoma, without Hypersplenic Cytopenia											
IX	X	XI	XII	XIII	XIV	XV	XVI				
C. E. V.	J. L.	J. R.	B. A. G.	H. K.	H. K.	C. O.	B. P.				
45 yrs.	67 yrs.	11 yrs.	62 yrs.	50 yrs.	38 yrs.						
'39	3/49	9/49	2/52	10/51	7/49	'46					
14 yrs.	4 yrs.	4 yrs.	18 mos.	4 yrs.	5 yrs.						
Cerv. ly. node 4/49 g.f.l.	Cerv. ly. node 8/52 ax. ly. node g.f.l.	Cerv. ly. node 2/52 cerv. ly. node g.f.l.	ly. sarcoma 7/49 cerv. ly. node g.f.l.	4/50 cerv. ly. node ly. sarcoma 4/46 c.l.n. g.f.l.	51 c.l.n. ly. sarcoma						
No	No	No	No	Yes 4 cm. below l.c.n.	Yes 4 cm. below l.c.n.	Yes					
Normal	Normal	Normal	Normal	Anemia	Normal	Anemia 24 ml.					
No	No	No	No	Yes 4 cm. below l.c.n.	Yes 4 cm. below l.c.n.	Yes					
No	No	No	No	No	No	No					
X-ray	X-ray	X-ray	HN <sub>2</sub> P <sub>32</sub>	HN <sub>2</sub> Aminopterin Cortisone	X-ray	X-ray					
V. good	Excellent	Excellent	V. good	Unknown	Unknown	Dec'd '51					



follicles and lymphosarcoma changes, which were interpreted by the members of the Department of Pathology, as well as by our Lymphoma Staff, as marking a transition from a benign phase to the more malignant phases of lymphoma at the time of this tissue study.

#### DISCUSSION

From a critical review of the medical literature dealing with "giant lymph follicle hyperplasia" certain very distinct impressions have been obtained: (1) This condition is usually reported as a clinical syndrome involving both lymph nodes and spleen, but without other specific features, and may be differentiated from other lymphomata only by microscopic tissue examination. (2) Very meager hematologic data have been obtained and relatively few bone marrow studies have been reported in patients with this diagnosis. (3) The outstanding histologic feature is follicular hyperplasia, which often shows prompt and prolonged response to x-ray, radioactive phosphorus, or other lymphopoietic suppressive therapy.

An analysis of the 104 reported cases (table 2) emphasizes the frequency with which an initial primary or accompanying splenomegaly was found at the time of the discovery of the first regional adenopathy. Since it has been observed in our clinics that many types of pathology, secondarily involving the spleen, may be followed by a more or less profound disturbance in the delicately balanced, reciprocal, hemolytotoxic equilibrium between bone marrow and spleen, the possible influence of the splenic involvement in primary giant follicle hyperplasia on the circulating blood cells has engaged our particular attention and has led to the specific discovery of the preceding cases.

The unique "giant-sized" follicular hypertrophy in the lymphoid tissues which has given the very descriptive name to this syndrome frequently may be recognized grossly as well as microscopically. In the earlier stages these "giant lymph follicles" are discrete (figure 1), but later they may fuse (figure 6) and break through their ordinary structural boundaries. While many authors have reported a characteristic chronicity and relatively benign clinical course with gratifying longevity in patients showing this initial histopathologic picture, Symmers,<sup>53</sup> Moschcowitz,<sup>43</sup> Held and Chasnoff<sup>29</sup> and Heinzelmann,<sup>28</sup> among others, warn that some individuals, who are first seen with an apparently simple functional lymph follicle hyperplasia, may terminate with clinical and hematologic pictures characteristic of lymphosarcoma, Hodgkin's syndrome or lymphatic leukemia. Since the etiology of no one of these dyscrasias, including giant lymph follicle hyperplasia, has yet been established, it may be that only superficial similarities appear on occasion to blend one or other of these respective entities into another, and that the fundamental cause of each is different, the course and

TABLE II

Case No.	Author	Date	Sex	Age	Duration in Months		Spleen (Gm.)	Lymph Nodes	Hg	R.B.C.	W.B.C.	Polys
					Before Rx	After Rx						
1	Kettle	1920	F.	34	2	28	800	Large		3.8 4.5	6,800 12,000	65 89
2	Josselin de Jong	1921	M.	53	2	12	1,500	Large	95 86	6.5 5.5	8,000 23,000	51
3			F.	34		144	6,500	Large		4.5	8,000	
4			M.	40		3	4,500	Large	30	4.5	8,000	
5	Brill et al.	1925	F.	32		12	1,800	Large	72	4.5 6.0	8,000	51 71
6	Ikeda	1926	F.	43	1	6	890	Large	70 75	3.9 4.5	900 6,550	30 51
7	Kellert	1931	F.	49	6	12	2,880	Large		3.0	6,200	65
8	Ross	1933	F.	56	12	24	4,500	Large	46 70	3.1 4.7	2,400 19,000	19 12
9	McNee	1934	F.	58	12	48	1,200	Large	75 102	3.7 5.1	3,300 8,500	55 55
10			M.	70	6		1,500	Large	30	2.5	3,000	
11	Berman et al.	1950	M.	26	3	5	1,300	Large		2.9 5.5	2,900 16,000	7

ultimate outcome in each patient being dependent upon a variety of complicating factors not yet known or suspected.

Whenever the finer cellular and tissue reactions in any disease have been subjected to detailed analysis by a variety of different technics, there has arisen an understandable difference of opinion—as to the specific cell types involved and their origins—between different investigators, and even in the thinking of the same investigator from one time to another. The tissue reaction to the same given insult may vary in time and degree from one patient to another; or, conversely, the cellular response to a number of different stimuli may at times be quite similar. The methods used to study the tissues—individual living cells, supravital stained, versus fixed, embedded and orthodox stained sections—may easily lead to diverse cell identifications and relationships. Thus, the cells which comprise the central zone of what appears to be a giant lymph follicle have been interpreted by some observers as reticulum (R-E) cell hyperplasia, by others as lymphoblastic proliferation.

TABLE II—Continued

Platelets	Bone Marrow	X-Ray	Reason for Splenectomy	Post Mortem	Additional Data
	None	None	Splenic anemia	None	Alive at last report.
Many	None	None	Not stated	None	Alive at last report.
	None	None	Not stated	None	Alive at last report.
	None	None	Not stated	None	Died 3 months after splenectomy.
	None	None	Not stated	None	Died 3 months after splenectomy.
160,000	Hyperplasia R.B.C.	None	Hemolytic anemia	None	Alive at last report. All criteria positive for hemolytic icterus. Splenic pulp congested.
150,000	None	None	Not stated	None	Alive at last report.
250,000	None	None	Not stated	None	Died one year—prolonged bleeding time.
40,000	Hyperplasia R.B.C.	None	Not stated	Complete	Died two years. Van den Bergh indirect.
	None	Ineffective	Cure "Sarcoma"	None	Alive at last report.
	None	None	Cure "Sarcoma"	None	Died immediately post-operative.
13,000	Hyperplasia	Ineffective	Purpura	None	Alive at last report.
1,000,000	Megakaryocytes	Ineffective			

The first report of a well studied case was made by Foix and Roemmele<sup>26</sup> in 1912. The nature of these elements was under discussion at that time: "One group feels that they originate in the reticulum cells, the other group feels that they originate from the endothelium of the blood vessels. . . . It is generally accepted in France that one is dealing with an endothelioma of a special type. One is struck by the presence of large numbers of cells which look neoplastic—their nuclei being very voluminous . . . making up approximately three-quarters of the entire cell volume."

Other European authors also feel that the reticuloendothelial cells are primarily involved. One of the most detailed descriptions of the cellular pathology, together with its possible significance, has been given by Ross.<sup>47, 48</sup> She writes: "Each nodule had a definite relation to a blood vessel which ran through it. The nodules did not consist of small lymphocytes but were composed of cells with large nuclei and relatively abundant cytoplasm. Still larger cells with vacuolated faintly stained cytoplasm were seen. The

nucleus was rounded with fine chromatin network and small nucleolus. Many cells contained eosinophilic globules which appeared to be the remains of red blood cells. The reticulum cells were enlarged and actively phagocytic. The bone marrow had the same structure as the lymph nodes and spleen." Kettle<sup>28</sup> and Robb-Smith<sup>46</sup> also have found evidence of phagocytosis of red blood cells. Among the contributors from the United States who mention the presence of phagocytosis of red blood cells are Baggenstoss,<sup>4</sup> Kellert,<sup>23</sup> Murray and Storr,<sup>44</sup> Cohen and Bergstrom<sup>14</sup> and Ikeda.<sup>30</sup> Caldwell<sup>12</sup> makes the statement that "ninety per cent of all cells in follicular lymphoblastoma are of the reticulo-endothelial type." Although Brill, Baehr and Rosenthal<sup>10</sup> first named the disease "generalized giant lymph follicle hyperplasia of lymph nodes and spleen," and considered the process benign, they later came to the conclusion that it is really a follicular lymphoblastoma and that the cells are malignant lymphoblasts. This has been the concept accepted by most writers in this country. We have studied 15 of the 16 cases in the present series with supravital staining of fresh tissue films, as well as in fixed sections. In our interpretation, the enlarged germinal center areas which characterized spleen and/or lymph nodes in these patients consisted of both R-E cells, some of which were highly phagocytic, and lymphoblasts. In four cases, typical lymphosarcoma cells appeared eventually as the predominating cell type, and in one instance the reticulum cells appeared to be assuming sarcoma characteristics. There is evidence that the multipotential basic mesenchyma in bone marrow, spleen and lymph nodes may give rise through the fixed reticulum elements to the free primitive cells from which monoblasts, lymphoblasts and myeloblasts differentiate,<sup>50</sup> and their sarcoma deviates may arise presumably by cell mutation. Any "stimulated" reticulum cell hyperplasia, then, will tend to increase the population of elements ready to differentiate according to the functional demands or opportunities of the particular tissue environment. We believe one function of the spleen to be that of a physiologic reservoir for the formed elements of the blood arising in the bone marrow. Enlargement of this organ *for any reason* may thereby increase its reservoir potential. There is good evidence<sup>22</sup> that excessive and prolonged parenchymal sequestration of any of the circulating blood elements will permit or cause qualitative chemical osmotic and/or mechanical fragility changes in the cells, rendering them more susceptible to premature phagocytosis by the R-E cells. Furthermore, the R-E cells have been described as at least one source of specific globulin antibodies—agglutinins and cytolytins—or as participating in their production.<sup>51</sup>

The spleen appears to be one of the first sites of germinal center reticulum cell hyperplasia in giant follicle hypertrophy. While both spleen and lymph nodes may and do enlarge, it is the vascular fenestrations,<sup>9</sup> found only in the spleen, which provide the unique sinusoidal-parenchymal storage depot for any or all blood cells. The need, and therefore the stimulus, may be presumed to be principally there for the primitive free R-E cells within the

germinal centers to realize their full phagocytic potential. Against such an enlarging reservoir, with its pathologic cell-sequestering potential, even the greatest hematopoietic efforts at production compensation by the bone marrow may at times prove inadequate. The promptness and permanence of the reestablishment of the hemolytotoxic reequilibration for granulocytes, erythrocytes and/or platelets, when such a vicious cycle is broken by successful splenectomy or accessory splenectomy, are strong circumstantial evidence in support of the unique cytoimmunologic-hypersequestration hypothesis of the hypersplenic state.

The first case in which splenectomy was performed for giant follicle hyperplasia was reported by Kettle<sup>35</sup> in 1920. This observer stated that the operation was recommended because of "splenic anemia," and that the patient was alive 28 months following operation. In the three cases reported by Josselin de Jong<sup>32</sup> in 1921, surgery was performed in the hope that the disease was localized to the spleen and that removal of this organ might induce a permanent cure, but the late results in these patients are unknown. Brill, Baehr and Rosenthal<sup>10</sup> published the first description of cases occurring in the United States, and their case 2 was subjected to splenectomy: "Because of increased weakness, progressive anemia and evidence of marked blood destruction *due to the large spleen* (our italics) it was decided to do a splenectomy to improve the condition of the patient." In discussing the pathology, the comment is made: "The pulp of the spleen is markedly congested, sinuses are dilated and the reticular tissue is increased." This patient "lived for many years" after splenectomy. In spite of the definite statement that the splenectomy was done because of evidence of "anemia due to blood destruction," their summary states that the disease is characterized by a "normal" blood picture. While it is evident that they meant only to emphasize that the disease is usually seen without intrinsic abnormality of any of the circulating white blood cells, most reviewers have since inferred that a "normal blood picture" is always characteristic of this condition.

The reason for splenectomy in Ikeda's<sup>30</sup> case is not specifically stated, but the fact that only 900 white blood cells were found preoperatively indicates a possible "hypersplenic" mechanism responsible for the peripheral leukopenia, especially since splenectomy was followed by a prompt recovery of the neutrophils and the patient was clinically improved and still alive 12 months after splenectomy. Kellert's<sup>33</sup> case is stated to have had a prolonged bleeding time, and therefore it could be presumed that splenectomy was done for thrombocytopenia. This patient died one year after splenectomy. Ross's<sup>47</sup> case was subjected to splenectomy for hemolytic phenomena and lived for two years after splenectomy. The two splenectomies reported by McNee<sup>38</sup> appear to have been advised for "sarcoma" of the spleen, though he refers to Ross's<sup>48</sup> cases, and may have meant to imply that his patients showed similar hemolytic phenomena. Berman et al.<sup>8</sup> splenectomized their

patient as a life-saving measure during an episode of fulminating secondary (hypersplenic) thrombocytopenic purpura. This patient was alive when reported upon five months after operation.

In our first case, splenomegaly was found before any peripheral blood changes, and then there were varying episodes of thrombocytopenia, granulocytopenia and anemia over a period of two and a half years before splenectomy was accomplished. There had been no progress of the primary disease or recurrence of the hematologic disturbance during the intervening nine months. The second patient showed acute hemolytic anemia before splenectomy, and has remained entirely free of any hypersplenic manifestations during the succeeding seven years. The third patient was first diagnosed in 1944 by lymph node biopsy, but it was not until June, 1949, that she developed an exceedingly acute secondary (hypersplenic) hemolytic crisis, for which emergency splenectomy was done and proved immediately corrective, a result which has been permanent to date. The fourth patient developed a subacute hypersplenic thrombocytopenic purpura which required splenectomy in 1945, the subsequent remission lasting three years. A recurrence, identical in all particulars with the first episode, was treated conservatively with repeated fresh whole blood transfusions for six months. At the end of this time surgical reexploration was undertaken and a 50 gm. accessory spleen removed, followed by restoration of the thrombocyte level to normal. No further purpuric manifestations have recurred. The fifth case is of seven years' known duration for the disease. Panhematopenia on a hypersplenic basis was indicated from bone marrow and spleen studies, and the reappearance following splenectomy of normal numbers of normal circulating blood cells would seem to confirm this mechanism as responsible. A syndrome typical of lymphosarcoma later resisted all therapeutic measures and was the ultimate cause of death.

The sixth case showed evidence of a hemolytic anemia at or soon after birth, since splenectomy was accomplished at four months of age. Following a year of hematologic remission, a generalized hyperphagocytic R-E cell hyperplasia of all lymphatic tissues developed, as proved by multiple biopsies, with a recurrent hemolytic type of anemia, currently under treatment by radioactive phosphorus. The seventh patient showed peripheral leukopenia and thrombocytopenia predominantly associated with his splenomegaly, and removal of the spleen initiated a clinical and hematologic remission lasting eight years. Currently, a suggestive reticulum cell sarcoma metamorphosis has been kept under control with radioactive phosphorus for 10 months. Our eighth patient presented with clinical and laboratory findings compatible with an acute primary, hypersplenic, thrombocytopenic purpura, and emergency splenectomy revealed the real underlying pathologic picture of giant follicle lymphoma. A six months' remission has followed to date.

In the eight patients in our series thus far showing no hypersplenic cytopenic manifestations, the disease has been under observation and treatment



for from 18 months to 14 years. In four of these individuals, lymphosarcoma or reticulum cell sarcoma changes have developed during this period.

The clinical course of giant lymph follicle hyperplasia as heretofore reported, and as observed in our own series, is relatively chronic and prolonged. Of the 104 cases reviewed, 23 were known to be living an average of five years after the diagnosis was established. Ten, followed from the time of diagnosis to fatal termination, survived an average of 4.4 years. The duration of the disease in the remaining 71 cases is not indicated, other than by "chronic course." Thirty patients were presented with insufficient evidence to evaluate their hematologic status; 34 were still living and under continued observation, without recognized signs of hypersplenism or change in pathologic status when reported. In the 52 cases studied until fatal termination or until splenectomy, 25 (or 48 per cent) had either suggestive or definite evidence of some one of the cytopenic, so-called "hypersplenic syndromes." Eighteen were subjected to splenectomy, of whom 14 were still living, and two had survived six and 12 years, respectively, at last report (table 2). In our series of 16 patients (table 1) eight (or 50 per cent) have been subjected to splenectomy for definite hypersplenic cytopenic episodes; of them, seven are presently living nine months to 10 years post-splenectomy.

#### CONCLUSIONS

1. A relatively benign, perhaps functional, R-E cell hyperplasia appears to underlie and to be responsible, at least in part, for the development of abnormally enlarged germinal follicular centers in the chronic splenolymphatic disease, descriptively designated as giant follicle hyperplasia, likewise known as follicular lymphoblastoma.

2. The specific cellular detail within these grossly and characteristically enlarged follicles varies from patient to patient, and in the same patient from time to time, as observed in the present series of 16 patients, and as interpreted from the medical literature. There may be a predominance of large fixed reticulum cells without pronounced phagocytic capacities, or free mononuclear phagocytes may be prominent, or cells interpreted as germinal center lymphoblasts may predominate, with or without sarcoma characteristics. The clinical course and individual prognosis may be predicted fairly accurately, depending upon the identification of these several morphologically and functionally (supravital technic) differing cell types.

3. When the spleen becomes involved and enlarged in one of these processes, hypersequestration of one or more of the circulating blood cell types frequently occurs, facilitated by the unique, vascular, sinusoidal-parenchymal reservoir system of this organ. An absolute peripheral cytopenia with characteristically related clinical manifestations may then develop if and when the bone marrow responds with a compensatory but ineffective hyperplasia of the specifically deficient circulating blood element or elements. The

suspected dysplenism may be confirmed through the successful surgical removal of the spleen, followed by the prompt reestablishment of a normal circulating cellular equilibrium. This occurred in all eight of our splenectomized patients, and an R-E cell hyperplasia with specific hyperphagocytosis was histologically demonstrated in the removed spleens.

4. If a recurrence of the original cytopenic syndrome develops, as in two instances reported in this paper, the presence of an accessory spleen should be suspected; and when this mechanism is at fault, surgical reexploration with the removal of the hypertrophied accessory splenic tissue will be followed by a second remission. Only rarely do the R-E cells participate in this hyperphagocytosis in tissues other than the spleen. When this does occur, as in the second of our two recurrences, specific suppressive therapy is required.

5. The relative ease with which x-ray or radioactive phosphorus therapy controls the benign type of follicular hyperplasia in lymph nodes and spleen justifies an optimistic prognosis in this disease, subject only to the complications mentioned. When sarcoma changes develop, as in four of the 16 patients in our series, the treatment and prognosis must be readjusted correspondingly.

6. The etiology or etiologies of "giant lymph follicle hyperplasia" are entirely unknown at the present time. The relatively benign character in at least some of these cases, however, suggests at times a reversible or controllable physiologic functional response rather than always a progressive, irreversible, pathologic-malignant mutation of the cells in the enlarged germinal centers.

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## THE CLINICAL EFFECT OF ISONIAZID AND IPRONIAZID IN THE TREATMENT OF PULMONARY TUBERCULOSIS\*

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SINCE the hydrazine derivatives of isonicotinic acid were first advocated as effective against tuberculosis early in 1952, there has been much serious appraisal of their therapeutic value. Isoniazid already has taken an important place in phthisiotherapy, if only because of the ease of its application and the small expense of the drug. But there is a need for extensive and prolonged clinical experimentation before the encouraging results of scarcely one year can be confirmed. Much of the early publicity campaign in the daily press about the new "miracle drugs" still lingers on, in the minds not only of the public but also of the medical profession. In this connection it is important to point out that, of the two isonicotinic acid derivatives which were introduced, namely, iproniazid (Marsilid) and isoniazid (Rimifon), it is the latter which now is in use almost exclusively, although wild initial claims of miracles performed originated chiefly from the experience with the former drug. The first two publications from Sea View Hospital<sup>1,2</sup> in New York reported on 92 patients, 81 of whom (88 per cent) had been treated with iproniazid and only 11 (12 per cent) with isoniazid. In a later paper<sup>3</sup> from the same institution, results in 175 patients were reported and again the majority of 106 (60 per cent) had received iproniazid and the minority of 69 (40 per cent) isoniazid. The widely heralded initial therapeutic success, taken at face value, must therefore be attributed to iproniazid rather than to isoniazid. In spite of spectacular symptomatic results, iproniazid has been used since in comparatively few instances and by now has lost its place to isoniazid almost entirely. The reason for this seems to be the greater frequency and severity of toxic side effects. It is the chief purpose of this paper to examine and evaluate the clinical usefulness and the pitfalls of iproniazid therapy in comparison with those of isoniazid.

One hundred fourteen patients in Montefiore Hospital and in its Westchester Division were treated with isoniazid and the combination of isoniazid and streptomycin over periods of from four to 12 months, or with

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iproniazid for from one to somewhat over six months (table 1). After a preliminary dosage of 2 mg. per kilogram, the dosage generally used was 4 mg. of isoniazid or iproniazid per kilogram of body weight; in some patients the isoniazid dosage was as high as 6 mg. per kilogram. In a few patients therapy was discontinued after only a few weeks because of severe toxic manifestations. Treatment was given both to patients who had and

TABLE I  
Treatment of 114 Patients

	Isoniazid	Isoniazid and Streptomycin	Iproniazid
Number of patients treated	27	53	34
Duration of treatment			
Range in months	4-12	4-12	1-6.5
Average	8.2	7.4	3.9

to those who had not previously received other chemotherapy, mostly with the combination of streptomycin and PAS. In approximately half of the group one of the new drugs, usually isoniazid, did not replace but was added to the streptomycin therapy. All patients were seen daily and were followed at appropriate intervals with posterior-anterior roentgenograms and tomograms of the chest, bronchoscopic examinations, bacteriologic study of sputum and of gastric contents by means of direct smear, concentrate and

TABLE II  
Effect on Cough

	Isoniazid	Isoniazid and Streptomycin	Iproniazid
No cough	8	31	5
Cough	19	22	29
No change	7 37%	7 32%	9 31%
Mild improvement	8 42%	9 41%	3 10%
Moderate improvement	2 11%	3 13%	9 31%
Marked improvement	1 5%	1 5%	7 24%
Worse	1 5%	2 9%	1 4%

culture, complete blood counts, urinalyses, sedimentation rates and liver function tests.

The symptomatic changes observed under the various regimens are recorded in tables 2 to 6. In the appraisal of all symptomatic improvements, especially in cough, sputum production and gain in body weight, it was kept in mind that good institutional bed-rest alone can be responsible for a large measure of them. The return of the body temperature to normal values is such a common occurrence in initially febrile patients with chronic



TABLE III  
Effect on Amount of Sputum

	Isoniazid	Isoniazid and Streptomycin	Iproniazid
No sputum	6	27	9
Sputum	21	26	25
No change	7 33%	9 35%	9 36%
Mild decrease	9 43%	6 23%	1 4%
Moderate decrease	4 19%	10 38%	1 4%
Marked decrease	1 5%	0 0	11 44%
Worse	0 0	1 4%	3 12%

TABLE IV  
Effect on Appetite

	Isoniazid	Isoniazid and Streptomycin	Iproniazid
Appetite initially good	18	34	0
Appetite initially poor	9	19	34
No change	5 56%	3 16%	13 38%
Mild improvement	2 22%	12 63%	6 18%
Moderate improvement	2 22%	3 16%	8 23%
Marked improvement	0 0	0 0	7 21%
Worse	0 0	1 5	0 0

TABLE V  
Effect on Weight

	Isoniazid	Isoniazid and Streptomycin	Iproniazid
No. of patients who gained	13 48%	29 55%	29 85%
No. of patients who did not gain	14 52%	24 45%	5 15%
Average gain of weight			
A—In those who gained	4.5 kg	4.0 kg	9.0 kg
B—Whole group	2.1 kg	2.1 kg	8.1 kg

TABLE VI  
Effect on General Condition

	Isoniazid	Isoniazid and Streptomycin	Iproniazid
Condition initially good	20	33	0
Condition initially poor	7	20	34
No change	3 43%	3 15%	20 59%
Mild improvement	1 14%	9 45%	2 6%
Moderate improvement	2 29%	5 25%	7 20%
Marked improvement	0 0	1 5%	4 12%
Worse	1 14%	2 10%	1 3%

tuberculosis after they have begun to rest that we refrained from recording such changes in this report. In view of this tendency to symptomatic improvement without drug therapy, the values recorded in the tables as "mild" have been included for the sake of completeness rather than out of a con-

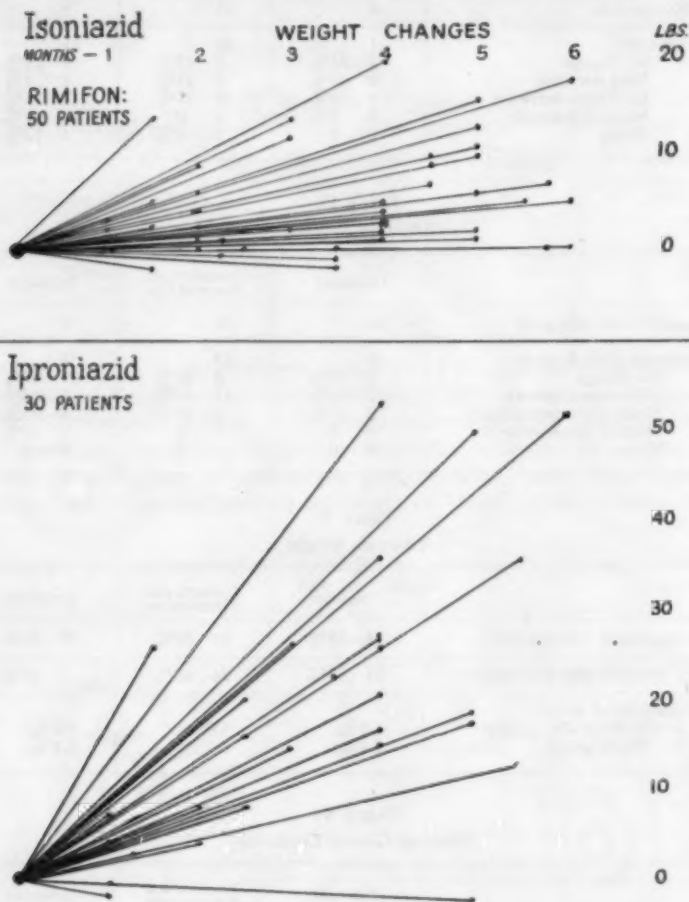


FIG. 1.

viction that they represent the effect of chemotherapy. To some extent this is true also of "moderate" improvements, and only the changes recorded as "marked" were much more pronounced than could be expected from bed-rest alone. From this viewpoint, iproniazid emerges as by far the most potent drug for alleviating the common symptoms of tuberculosis. Cough

and expectoration (tables 2 and 3) were diminished in more than half of the patients, and sputum production vanished completely in a few; the appetite (table 4) increased in about an equal number and expressed itself in striking increases in body weight (table 5). A few patients gained 50 pounds or more during a six month period (figure 1). Some of this gain—but only a small part—is to be attributed to moderate edema, which promptly disappeared when the drug was discontinued. Improvement of the general condition (table 6) expressed itself essentially as a sense of well being; this, in some patients, seemed to be at least as much the result of iproniazid-induced mental and emotional changes as of genuine physical improvement. Symptomatic changes differed little in the two groups of patients treated with isoniazid and with the isoniazid-streptomycin combination. Both were only moderately effective, when the salutary action of bed-rest alone is also taken into account. In a considerable number of patients treated with isoniazid alone, initial improvement of symptoms was soon followed by a reversion to the pretreatment symptomatic status. This did not occur with the combination of isoniazid and streptomycin, which seems to have produced much more lasting results, confirming the results reported by others.<sup>4</sup> In spite of this experience the combined isoniazid-streptomycin treatment has the disadvantage of inducing bacterial resistance to both drugs simultaneously. We agree with the suggestion that in patients who are expected to need surgical therapy the preservation of bacterial sensitivity for postoperative chemotherapy is of sufficient importance to give preference to preoperative treatment with one of the drugs in combination with PAS, to which the other should be added postoperatively.<sup>5</sup>

TABLE VII  
Effect on Sputum Conversion

	Isoniazid	Isoniazid and Streptomycin	Iproniazid
Pretreatment sputum negative*	10	16	4
Pretreatment sputum positive	17	37	30
Sputum conversion	4 24%	20 54%	13 43%
No sputum conversion	13 76%	17 46%	17 57%

\* All patients were sputum-positive before or on hospital admission.

The effect on bacillary content of the sputum was significantly greater with isoniazid and streptomycin than with either isoniazid or iproniazid alone (table 7). Sputum conversion judged by culture tests was attained in more than half of the patients who received the combined therapy. It would be premature at this time to attempt judgment on the comparative effect of streptomycin and the isonicotinic acid derivatives solely on sputum conversion. Likewise, experience with the development of bacillary re-

sistance is just now being gathered. Sensitivity tests for isoniazid gave the following results:

Ninety cultures of sputum and/or gastric contents from 33 patients receiving isoniazid alone have been tested for *in vitro* sensitivity to the drug. The organisms were grown initially on Petragnani medium, then transferred to Tween-albumin medium, and a two weeks old culture in liquid Tween-albumin medium was inoculated into solid Petragnani medium containing 1, 10 and 100 micrograms of isoniazid per cubic centimeter. The drug was added prior to coagulation at 85° C. for 45 minutes.

In 25 of 31 patients whose cultures were tested before institution of isoniazid treatment, the organisms were found sensitive to 1 microgram of isoniazid per cubic centimeter. In four, the organisms were resistant to 1 microgram per cubic centimeter, but sensitive to 10. In one, they were resistant to 100 micrograms; this patient had received iproniazid for nine months previously. In one patient two different cultures tested before treatment gave contradictory results, with the organism growing in the presence of 1 microgram per cubic centimeter of the drug in one culture but apparently sensitive in the other.

The culture of one patient who had received isoniazid for seven months and who had had no pretreatment culture tested showed organisms resistant to 1 microgram per cubic centimeter, but sensitive to 10 micrograms per cubic centimeter. In another case, which likewise had had no pretreatment culture tested, a culture inoculated six weeks after institution of treatment was resistant to 100 micrograms per cubic centimeter.

Of the 25 patients whose organisms were sensitive to 1 microgram in the pretreatment culture, adequate follow-up sensitivity tests have been performed in six. Of these, two were sensitive to 1 microgram after six weeks of treatment, one was resistant to 1 microgram but sensitive to 10 after one month of treatment, and two were resistant to 100 micrograms per cubic centimeter after receiving the drug for three months. In one case cultures were resistant to 1 microgram per cubic centimeter after seven weeks of treatment, and resistant to 100 micrograms after five months of treatment, but were again sensitive to 1 microgram per cubic centimeter in a specimen collected 16 weeks after isoniazid administration had been discontinued. Findings similar to those in this latter case have been reported by Knox.<sup>6</sup>

In view of the unresolved questions concerning the technic of these tests, the data are merely recorded and no conclusions are drawn.

Encouraging as were the initial symptomatic improvements, especially with iproniazid therapy, the healing effect on chronic pulmonary tuberculosis as observed by serial x-ray examinations was disappointing (table 8). In a large percentage of patients in whom definite improvement was noted roentgenologically, this did not exceed the favorable changes, either in extent or speed, or both, which can occur on bed-rest only. In general, improvement from either of the new drugs alone did not measure up to that achieved with the streptomycin-PAS combination, and in no case was it

TABLE VIII  
X-Ray Changes

	Isoniazid	Isoniazid and Streptomycin	Iproniazid
No change	19 71%	30 56%	19 55%
Mild improvement	0 0	10 19%	6 18%
Moderate improvement	6 22%	10 19%	3 9%
Marked improvement	2 7%	2 4%	2 6%
Worse	0 0	1 2%	4 12%

striking enough to be rated as superior to those resulting from the older drugs. Impressive improvement in the pulmonary pathology was limited to the fresh exudative and exudative-caseous forms of the disease, as has been observed in all drug therapies which have been introduced so far. The

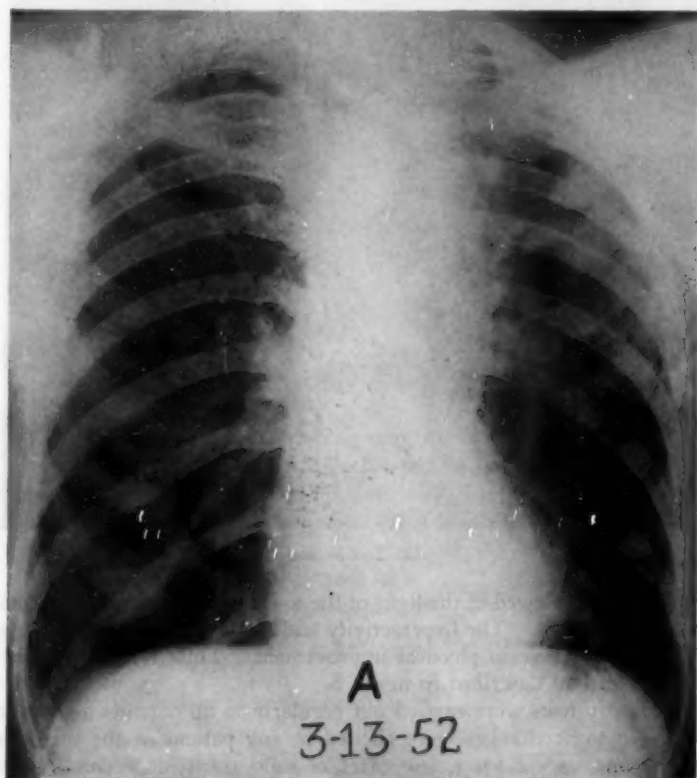


FIG. 2.

best single result was achieved with iproniazid in the patient described in figure 2.

We believe that the effect of chemotherapy on cavity closure has been overstated and that the deflation and inspissation of pathologic defects is as much—and probably more—the result of diminished respiratory effort on rest as it is due to the influence of drugs. The comparatively poor results with iproniazid, especially in cases of progressive disease under

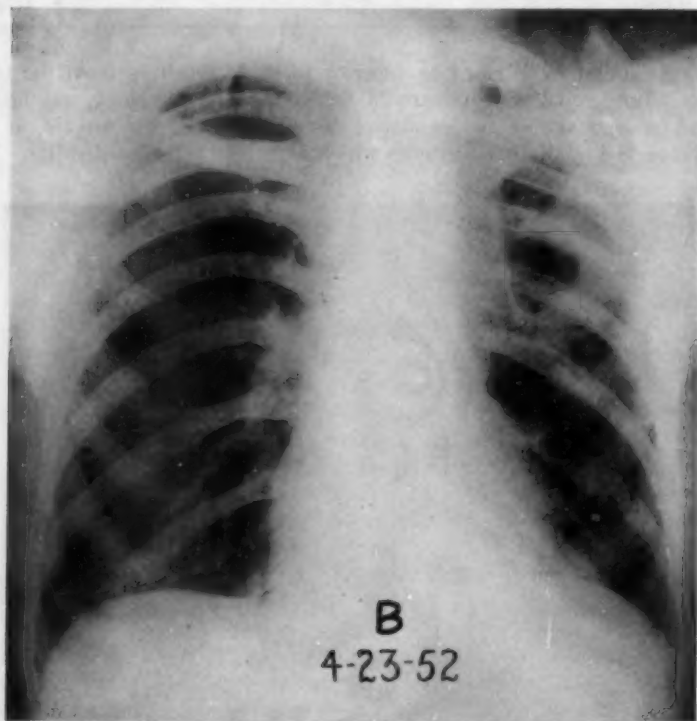


FIG. 2—Continued.

therapy, must be viewed in the light of the toxic side effects on the emotional status of the patient. The hyperactivity and restlessness caused by the drug may nullify and reverse physical improvement. This is illustrated by the case of the patient described in figure 3.

Laboratory tests were carried out regularly in all patients as mentioned above. No toxic changes were elicited in any patient in the three therapeutic groups, except for a few cases of mild transient anemia. Clinical toxic manifestations were infrequent, of minor degree and temporary in both



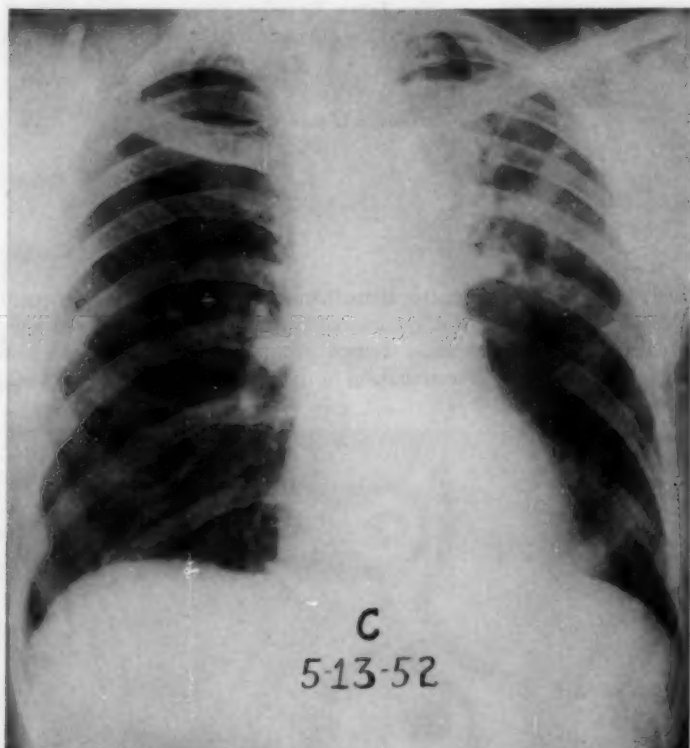


FIG. 2—Continued.

the isoniazid and the isoniazid-streptomycin treated groups (tables 9 and 10). In contrast, the toxic symptoms from iproniazid were numerous, occurring in 68 per cent of the patients treated with this drug. While the manifestations other than those in the central nervous system (table 11) were com-

TABLE IX  
Toxicity of Isoniazid Therapy

Number of patients	27	
No toxicity	25	93%
Toxicity	2	7%
4 toxic manifestations in 2 patients		
Nausea	1	
Rash	1	
Headache	1	
Insomnia	1	

TABLE X  
Toxicity of Isoniazid and Streptomycin Therapy

Number of patients	53
No toxicity	40 75%
Toxicity	13 25%
12 toxic manifestations in 13 patients	
Rash	1
Headache	4
Constipation	2
Restlessness	1
Insomnia	3
Muscle twitching	1

paratively mild, neuropsychiatric disturbances (table 12) were frequent, in many cases pronounced, and occasionally threatening. Twenty per cent of the patients in the iproniazid-treated group suffered psychotic episodes. These usually cleared with termination of drug therapy (case 1, figure 2).

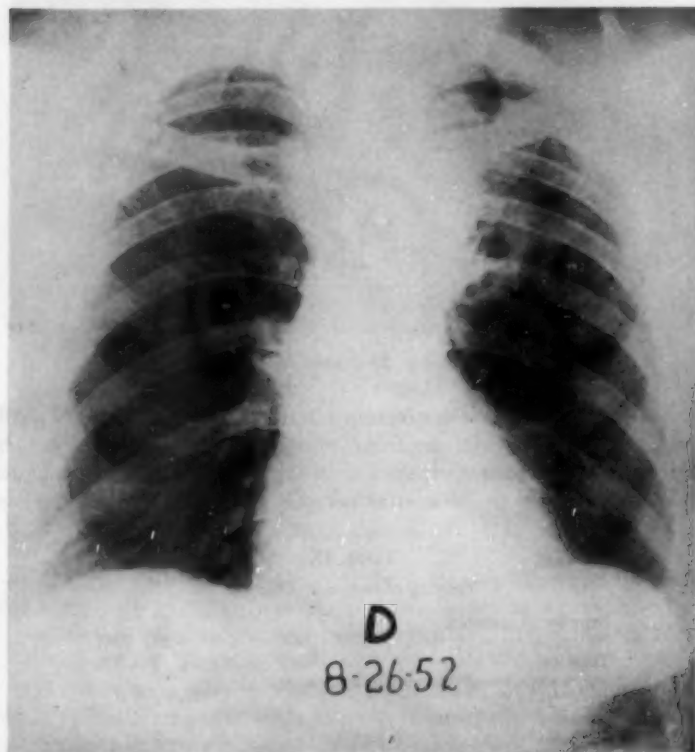


FIG. 2—Continued.

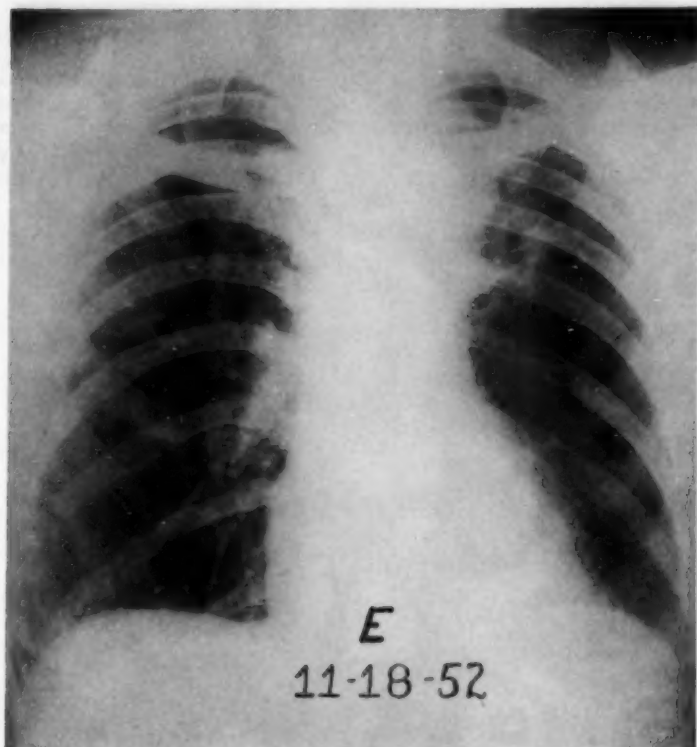


FIG. 2—Continued.

TABLE XI  
Iproniazid Toxicity

Total number of patients	34
No toxicity in 11 patients	32%
Toxicity in 23 patients	68%

*74 toxic manifestations in 23 patients*

## Manifestations Other Than in Central Nervous System

	Mild	Severe	Total
Skin eruption	4	0	4
Constipation	1	1	2
Difficulty in urination	5	0	5
Dyspnea	4	0	4
Edema	9	0	9
Disturbance from adjuvant drugs	0	5	5
Total Number	23	6	29

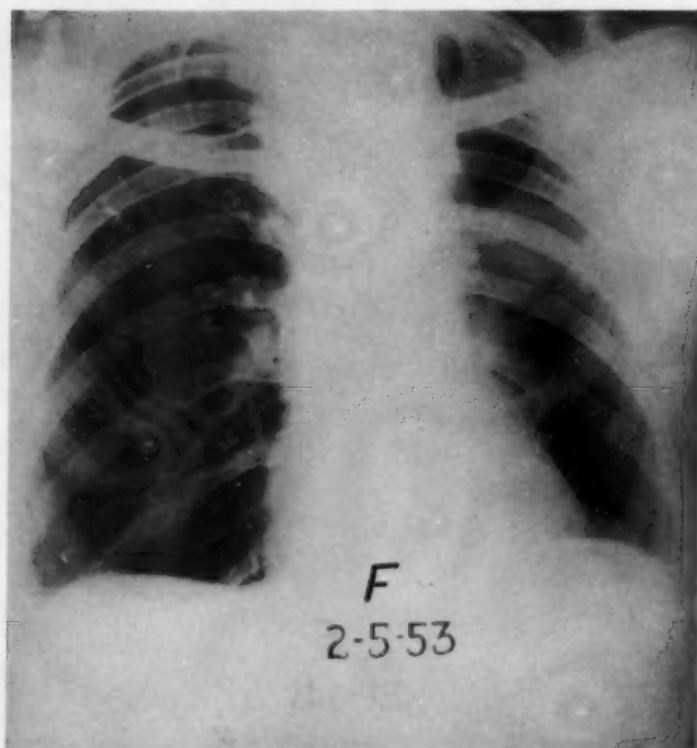


FIG. 2—Continued.

TABLE XII  
Iproniazid Toxicity  
Neuropsychiatric Manifestations

	Mild	Severe	Total
Dizziness	7	0	7
Blurred vision	3	1	4
Tremors	6	2	8
Inability to concentrate	0	1	1
Tension	0	1	1
Irritability	0	3	3
Insomnia	7	1	8
Nightmares	1	0	1
Hallucinations	1	0	1
Euphoria	0	3	3
Depression	1	0	1
Manic psychosis	0	5	5
Paranoid psychosis	0	2	2
Total Number	26	19	45

*Case 1* (figure 2). R. G., a 41 year old married Negro female, was admitted to Montefiore Hospital March 13, 1952 (figure 2-A). The onset of her disease was in November, 1951, with chills and fever to 104° F. A roentgenogram of the chest showed tuberculosis of the left upper lobe with extensive cavitation. Sputum was positive on smear for tubercle bacilli. While she was a patient at another hospital she had received streptomycin, 1.0 gm. daily, and PAS, 10 gm. daily, from January 25, 1952, to February 28, 1952, without effect. Fever continued to 103° F. daily.

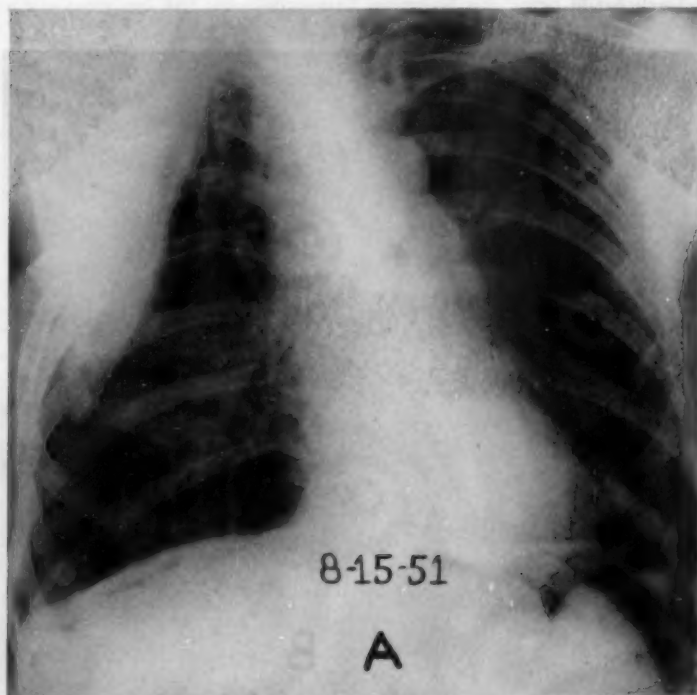


FIG. 3.

Physical examination on admission revealed dullness to percussion and râles over the left upper chest. Isoniazid, 2 mg. per kilogram (100 mg.), was begun April 7, 1952, and increased to 4 mg. per kilogram (200 mg.) on April 10, 1952 (figure 2-B). After 10 days of isoniazid therapy the patient became afebrile. Her general condition rapidly improved and she began to gain weight (figure 2-C). After four weeks of therapy the patient developed a pruritic macular eruption on the thighs, arms and shoulders, insomnia and dizziness. One month later she developed 2 plus pitting edema of the legs. On August 12, 1952, the patient developed an acute paranoid state with depression, desire for withdrawal and repeated crying bouts. She had paranoid ideas about other patients on the ward. Apparently this reaction had been building up for about two months. For this reason, on August 14, 1952 (figure 2-D) iproni-

azid was discontinued and the psychotic reaction disappeared. The disease in the left upper lobe regressed markedly and the cavities became much smaller. Her sputum remained positive on culture for tubercle bacilli. She gained 53 pounds in weight and became afebrile, and her general condition improved markedly. On August 15, 1952, she was started on streptomycin, 1.0 gm. three times a week, and PAS, 10 gm. daily. On November 24, 1952 (figure 2-E) the patient underwent a left upper lobe lobectomy without incident. Since the operation she has done well and is being gradually rehabilitated (figure 2-F). Her sputum is now negative on culture for tubercle bacilli.

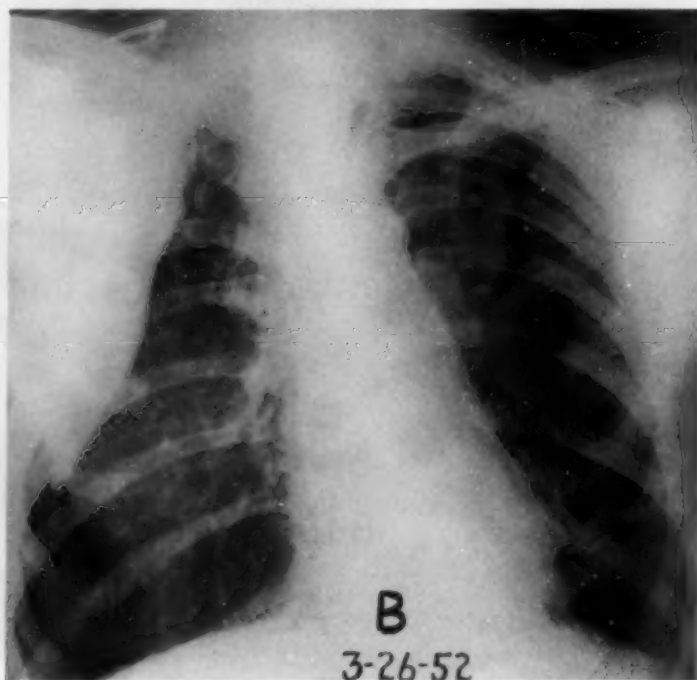


FIG. 3—Continued.

One patient has been confined in an institution for mental diseases ever since the onset of a psychosis eight months ago. The pertinent data of his case history follow:

*Case 2 (figure 3).* T. F., a 58 year old white male, was admitted to the Westchester Division on July 23, 1951, suffering from moderately advanced fibrocavitary tuberculosis of the right upper lobe, and from less extensive involvement of the left upper lobe. The sputum was positive for tubercle bacilli on culture. The patient gave a history of alcoholism since the age of 21, but denied the use of alcohol for one year prior to admission. The summary of psychiatric evaluation on admis-



sion was as follows: "A 58 year old man in very good contact with his environment. No apparent deterioration is present but more or less inadequate euphoria colors the whole picture. No clear-cut neurotic mechanisms are elicited."

The patient was treated with bed-rest and streptomycin sulfate, 1.0 gm. daily, from November 5, 1951, to February 11, 1952, when the dosage was reduced to 1.0 gm. twice weekly. He also received 15 gm. daily of sodium PAS from November 5, 1951, to May 17, 1952. The response to this regimen was not remarkable. On May 17, 1952, administration of sodium PAS was discontinued, but twice-weekly streptomycin was continued, and administration of iproniazid was begun in dosage of 2 mg.

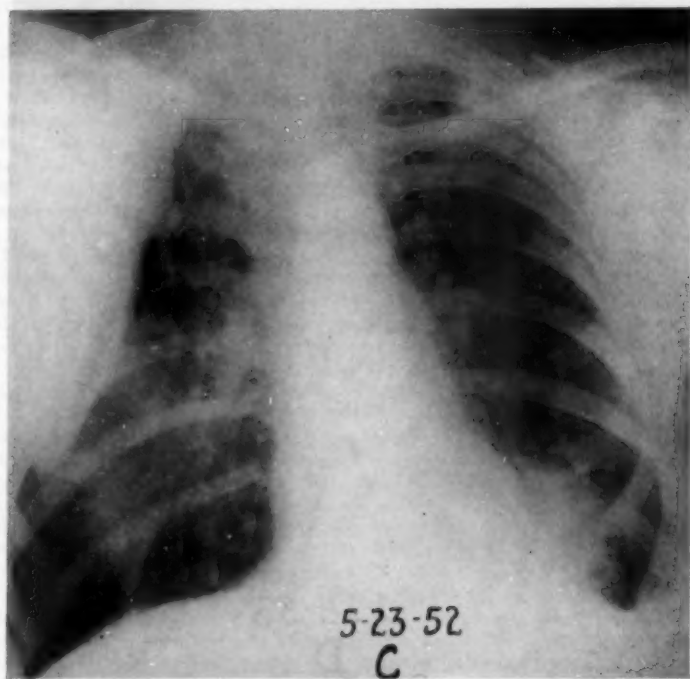


FIG. 3—Continued.

per kilogram per day. One week later the dosage of iproniazid was increased to 4 mg. per kilogram per day, or 225 mg. daily. Within the first two weeks on iproniazid therapy the body weight, which had been decreasing slowly, began to rise, and the patient felt generally well. During the fourth week of therapy slight pitting edema of the feet and legs appeared.

During the fourth week the patient showed increasing restlessness, which progressed in the next two weeks through a stage of hyperactivity, with marked euphoria and garrulousness, to a definite hypomanic state. He stated that he had "never felt so fine in my life. . . . This new drug is really a miracle." The physical as well as the vocal hyperactivity increased progressively, and in the seventh week of iproniazid

therapy, despite continued administration of the drug and the presence of a ravenous appetite, he began to lose weight, returning to his pretreatment level during the next three weeks. It was felt that his unusual physical exertions under the influence of the drug might have been responsible for the weight loss. He became increasingly unmanageable, and produced large volumes of written material which showed marked flight of ideas and lack of insight. Iproniazid was discontinued in the ninth week but the psychosis failed to improve, and on September 3, 1952, he was transferred to a psychiatric institution where the diagnosis of manic psychosis was confirmed.

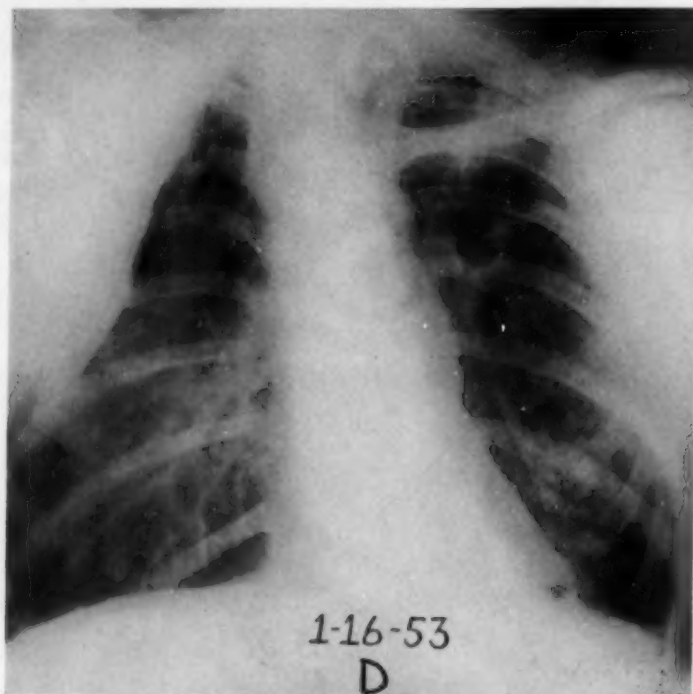


FIG. 3—Continued.

It was our impression, as well as that of the psychiatric consultants, that the frank psychotic episode was induced by iproniazid in a personality with some predisposition.

During the period of drug administration serial roentgenograms made every two weeks showed no improvement in the pulmonary lesion.

In some patients the neuropsychiatric complications, through hyperactivity and restlessness, thwarted the physical benefit which was derived from drug therapy. This paradoxical occurrence of the administration of an effective drug leading to new progression of the tuberculous process, has already been mentioned (case 3, figure 3).

*Case 3* (figure 3). D. F., a 31 year old single white male, was admitted to Montefiore Hospital August 14, 1951 (figure 3-A). There was a history of known pulmonary tuberculosis since 1942, and therapy had included bed-rest, streptomycin and PAS, pneumoperitoneum, right phrenemphraxis and right thoracoplasty. On admission his general condition was fair. He was markedly underweight and had a severe productive cough. Roentgenograms revealed extensive bilateral fibrocaceous cavitory lesions. Streptomycin and PAS were started but, despite this, the trend of his disease was slowly progressive. On March 22, 1952 (figure 3-B), these drugs were discontinued and eight days later administration of iproniazid was started in dosage of 2 mg. per kilogram per day for the first week, and thereafter 4 mg. per kilogram per day (225 mg.). The patient felt subjectively improved from the second week of treatment. There was marked increase in appetite and a weight gain of 50 pounds in six months. His cough and expectoration decreased, but sputum remained positive on smear for tubercle bacilli. Side effects of the drug included transitory mild anemia, clonic involuntary movements of the lower extremities, difficulty in initiating urination, and 1 plus pitting edema of the feet and legs. The pulmonary lesions showed no improvement, and during the third month of therapy slight progression of the left upper lobe lesion was noted. A small intrapleural effusion on the left side appeared during the eighth week of therapy and reabsorbed spontaneously during the subsequent eight week period (figure 3-C). Whether this was due to fluid retention or activity of tuberculous pleuritis has not been established.

Three weeks after iproniazid therapy was instituted a marked change in mood was apparent. The patient became elated, very talkative and hyperactive, and had difficulty staying in bed. On questioning he admitted to being unable to sleep but stated that he felt better than he had in years and that the insomnia did not disturb him. He also observed that he now was in a position to evaluate the effect of this new drug, which he considered remarkable, and asked for permission to address the other patients on the sanatorium radio to explain its effects to them. Physical and vocal hyperactivity became progressively more marked, to a point where the patient was spending practically all of his time pacing the corridors and lecturing to other patients whenever he found the opportunity. His general mood was one of elation and great physical well being, at a time when all objective evidence showed continuing activity and progression of his tuberculosis. During the fifth month of therapy the euphoria and hyperactivity decreased and were replaced by depression. At this time he wrote a letter to one of the authors (A.S.D.) in which he stated: "First of all I want to tell you how pleased I am at the remarkable progress effected since I have been on the new drug. There is, however, one disturbing side effect which, as you know, has been causing me some concern in recent weeks, namely, depressive moods of such intensity as to evoke uncontrollable sobbing, abject despair and thoughts of suicide. Another side effect of the iproniazid is a super-abundance of energy which has made it practically impossible for me to remain in bed for long periods of time. I have, in recent weeks, become interested in gardening as a hobby, and this has kept me mentally and, to a moderate extent, physically occupied. The recreational satisfaction derived from this pursuit has been great, and since the expenditure of physical energy involved is relatively small, I trust that you will allow me to continue."

Some of his verbal productions during psychiatric interviews are of interest. During the second month of therapy he stated: "I do not know how I am inside, but I feel 200 per cent improved because of the gain of weight (34 pounds) and also that feeling of well being. Previous to that I was always sluggish and tired. The drug gives you an unusual amount of energy. The first two or three weeks it gives you so much energy it really makes you feel strong, stronger than when I was well. That feeling of well being makes you sense that something is happening in your system

and makes you more optimistic about it." At this time the psychiatrist noted: "It is very difficult to evaluate the personality make-up of this individual and to what extent the hypomanic features that he presents could be attributed to the effects of the drug, or is merely a reactional factor built up on a previously existing personality. The patient appears to be mildly elated and talks profusely about the marvelous results of this wonder drug." One month later the psychiatrist noted that the "extreme happiness" about the "magical qualities" which the patient attributed to the drug were disappearing, and "a cooler approach to the situation is taking place." One month subsequent to this, during the fifth month of therapy, the patient stated: "I have been taking the drug for quite a while, and I had a severe attack, like a breakdown, Saturday night. I sat there and all of a sudden this intense depressed feeling came over me. I felt alone. There was nothing I could do. I started to cry, and it was the first time I cried since my mother died. H. (a nurse's aide) came in and comforted me. I felt as if I were going to crack up, and I felt I just had to be around people."

Because of the manic-depressive reaction, the drug was discontinued January 16, 1953 (figure 3-D).

The occurrence of untoward incidents during anesthesia or through the combination of iproniazid with other drugs also was observed. It is illustrated by the following case (case 4).

*Case 4.* J. B., a 31 year old married Negro female, was admitted to the Westchester Division in March, 1948, with bilateral upper lobe pulmonary tuberculosis. The lesion in the left upper lobe progressed and excavated on bed-rest. Despite an attempted left pneumothorax, streptomycin, PAS and Amithiozone ("Tibione") therapy the cavity remained patent and the sputum was intermittently positive for tubercle bacilli. In January, 1951, a resection of the apico-posterior segment of the left upper lobe was performed. Postoperatively there was extension of the disease to the anterior segment of the left upper lobe, associated with tuberculous bronchitis. Because of the failure of streptomycin to control the extension of the disease, iproniazid therapy was started on April 2, 1952. A dosage of 2 mg. per kilogram of body weight was used because, prior to treatment, the patient had had abnormal liver function tests. Side effects were noted in the first month of therapy, including insomnia, acneform eruption of the face and chest, and blurring of vision on standing. On September 11, 1952, the patient was prepared for bronchoscopy by spraying the posterior pharynx with 10 per cent cocaine and intratracheal installation of approximately 4 c.c. of a 1.3 per cent cocaine solution. The patient had had seven previous similar preparations for bronchoscopy without incident. Immediately after preparation she complained of a generalized "trembling sensation," palpitation, limpness of the legs, dyspnea, and blurring of vision which progressed to temporary blindness. The symptoms all disappeared spontaneously and iproniazid was discontinued. Three and one-half weeks later the patient was rebronchoscoped without incident. It was recalled that the patient had had two similar reactions to Novocain given for dental purposes while on iproniazid treatment. Prior to this drug therapy, Novocain used for dental purposes had caused no reaction.

Under iproniazid therapy there was slight clearing of the pulmonary and endobronchial disease, but the sputum remained positive.

It was observed that most of the patients who exhibited neuropsychiatric complications had been predisposed by at least mild neuroses or a labile emotional status. Patients of stable emotional status have been receiving iproniazid therapy for many months without any complications affecting

the central nervous system. We therefore do not agree that iproniazid therapy should be discarded, but believe that the patients receiving it should be selected with great care, possibly with the assistance of a psychiatrist, and that treatment should be administered under constant institutional observation. If these precautions are observed iproniazid can serve a very useful purpose in the treatment of greatly debilitated patients in whom speedy improvement of their general physical condition is of paramount importance through increase of appetite, gain of weight and, last but not least, restoring a sense of well being and confidence in their ability to fight the disease.

#### SUMMARY AND CONCLUSIONS

1. Isoniazid and iproniazid exert a definite beneficial effect in human tuberculosis symptomatically, pathologically and bacteriologically.

2. The symptomatic effect of iproniazid exceeds by far that of isoniazid and other antimicrobial agents or their combinations now in use. It expresses itself in striking increases of appetite, weight and sense of well being, and in a decrease of pulmonary symptoms.

3. Impressive improvement of pulmonary pathology is essentially limited to cases of exudative and exudative-caseous tuberculosis.

4. The healing effect of either drug alone did not measure up to that of the streptomycin-PAS combination.

5. The roentgenographic results with the isoniazid-streptomycin combination were not superior to those obtained with isoniazid alone, but seemed to be more lasting after therapy was discontinued.

6. Combined isoniazid-streptomycin therapy is not recommended for patients for whom surgical therapy is under consideration: bacterial sensitivity to one drug should be preserved for the postoperative course.

7. Sputum conversion was achieved in over 50 per cent of the patients with combined isoniazid-streptomycin therapy; with isoniazid alone, it was less than half that figure. Iproniazid therapy converted the sputum in over 40 per cent.

8. The development of bacterial resistance to isoniazid cannot be questioned. Detailed information as to the degree and speed of this occurrence could not be obtained from the data which have become available so far.

9. The toxic manifestations of isoniazid were of minor degree; those of iproniazid were numerous, often pronounced, and frequently affected the central nervous system. Neuropsychiatric changes were observed in emotionally labile individuals. Psychosis occurred in 20 per cent of all iproniazid-treated patients.

10. Iproniazid should be approved for the treatment of carefully selected patients in whom pronounced symptoms and a poor physical status require the speediest possible improvement of their general condition. Its administration should be permissible only under constant institutional care.

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## DIAGNOSIS AND TREATMENT OF AMEBIC LIVER ABSCESS \*

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THAT diagnostic difficulties are attendant upon the management of amebic liver abscess is attested by the frequency with which the condition is discovered at autopsy when the clinician did not suspect its presence. In a group of 40 autopsy cases of liver abscess due to amebiasis studied at the Armed Forces Institute of Pathology the attending physician had the correct diagnosis in but seven (17.5 per cent). Invasion of the liver undoubtedly occurs in every patient with amebiasis, and many patients with amebiasis have a large, tender liver (hepatomegaly) (43 to 50 per cent).<sup>1</sup> However, the incidence of liver abscess in amebiasis is much less (1 to 18 per cent).<sup>2</sup> The probable explanation of this phenomenon is that advanced by Rogers,<sup>3</sup> of presuppurative hepatitis.

It is agreed that the diagnosis of amebic liver abscess is upon firm ground only when the amebas have been demonstrated in the exudate or by a biopsy from liver or pleura. However, this is an unsatisfactory criterion from the clinical point of view, because adequate therapy should result in resolution of the abscess without need for surgical intervention. Furthermore, when material is obtained from an abscess, demonstration of amebas in the exudate is frequently not possible.

The diagnostic criteria employed by us are:

1. The presence of the clinical syndrome of amebiasis.<sup>1a</sup>
2. Demonstration of amebic intestinal lesions by sigmoidoscopic technics or demonstration of *Endamoeba histolytica* in aspirations or stool.
3. Objective evidence of focal hepatic involvement.
4. Unequivocal response to appropriate therapy.

These criteria are essentially in agreement with those established by others,<sup>2b, 3, 4</sup> except for our insistence upon the presence of the clinical syndrome of amebiasis and evidence of intestinal disease by demonstration of typical lesions or organisms. Fifteen cases of amebic liver abscess fitting these criteria have been seen by me during the period 1948-1953, and an analysis of their symptoms, physical and laboratory findings and treatment is the basis for the present report. Four of the cases involved in this report were seen at Fort Knox and 11 at Tokyo Army Hospital; eight were United States military personnel, three were United States civilian personnel and four were United Nations military personnel.

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The data with respect to the way these cases fitted the diagnostic criteria established are presented in table 1.

TABLE I  
Diagnostic Criteria Applied to 15 Cases of Amebic Liver Abscess

	Positive
Criterion 1	
Clinical syndrome of amebiasis	15
Criterion 2	
<i>E. histolytica</i> in stools or aspirations	12
Intestinal lesions present—negative for <i>E. histolytica</i>	3
Criterion 3	
Elevated diaphragm	2
Elevated diaphragm with pleuropulmonary involvement	8
Palpable abdominal mass	3
Abdominal mass by x-ray	1
Spontaneous rupture of liver abscess	1
Criterion 4	
Unequivocal response to therapy	15

In analyzing the clinical aspects of these cases, searching for clues to improve the accuracy of the diagnosis, it became apparent that many of the patients (11) had actually complained of sharply localized pain over some part of the liver, usually anteriorly, and that palpation of the hepatic area disclosed that this area was also the area of maximal tenderness. The other cases (four) complained of diffuse hepatic pain. In all cases the pain radiated to the back, usually straight through, although in two cases it ran around the rib margin. In six cases this pain also radiated to the clavicle. Palpation disclosed the area of maximal pain to be the area of maximal tenderness, and pressure here reproduced the radiation of pain to back and clavicle. The liver was palpably enlarged in all cases. The pain was constant and often described as sharp. In all cases it was aggravated by movement, jarring or a deep breath. All of the patients lost weight (more than 30 pounds in 10 cases), and all had fever. In three cases an abdominal mass was palpable. In one of these the mass was fluctuant. In one case edema of the overlying skin and subcutaneous tissues was observed. In one instance the spleen was palpable. All of these cases had intestinal lesions visible on sigmoidoscopic examination, ranging from superficial erosions and miliary abscesses to large ulcerations and, in one case, a 5 by 7 cm. ameboma of the rectum.

X-ray examination of the chest was most helpful and revealed elevation of the diaphragm in 10 cases, eight of these having overlying pleuropulmonary involvement. In one case a liver abscess in the left lobe was demonstrated pushing the barium filled stomach to the left. In two cases ancillary evidence of intestinal involvement was demonstrated by barium enema. Leukocytosis above 13,000 was demonstrated in all but one of these cases, and all of them had elevation of the erythrocyte sedimentation rate. Note-

worthy is the frequency with which liver function tests remain within normal range. Such tests were done on 12 of the cases and were normal in six; bromsulphalein retention was present in six, and elevated icterus index in four. Pleural aspirations and sputum were positive for *E. histolytica* in one case each, sigmoidoscopic aspirations in nine and stool examination in three cases each. No amebas were demonstrated in three cases, two of which had received prior antiamebic therapy. Four of these cases had received antiamebic therapy prior to coming under my observation. In one case this consisted of Aureomycin given under the mistaken diagnosis of bacterial pneumonia, one case received emetine alone, while one case received Terramycin and carbarsone, and the fourth case received chloroquine alone.

All of these patients were treated with atabrine and carbarsone according to the following plan: Atabrine, 0.1 gm. four times daily, was given for 30 days, combined for the first 10 days with carbarsone, 0.25 gm. twice daily for female and small male patients, and thrice daily for the average adult male. At the end of 20 days the patient was sigmoidoscoped, and if aspirations contained amebas, or unhealed intestinal lesions were seen, a second course of carbarsone was given. If the liver was enlarged or tender at the end of 30 days, Atabrine was given until this cleared up.

The 15 cases all had post-treatment follow-up of 30 days or more, with a minimum of two post-therapy sigmoidoscopic examinations.

Eight of the cases received 30 days of Atabrine therapy, and seven received more, the longest course being 56 days. Three of the cases required an additional course of carbarsone, two because of isolation of *E. histolytica* after 20 days of therapy, and one because of demonstration of unhealed intestinal lesions. Two of the cases required surgical drainage of the abscess cavity. One of these was complicated by the presence of hepatic carcinoma. However, *E. histolytica* was demonstrated in the material evacuated from the subdiaphragmatic space, and the surgeon demonstrated a liver cavity at operation after 24 days of Atabrine therapy, so it is presumed that activity of the abscess would have necessitated surgical evacuation without the presence of carcinoma. This is the only case of the group that died, and since no activity of the amebic process was demonstrated at post-mortem examination it is my belief that this should not be considered as a death due to amebic infection. Two of the cases with severe pleuropulmonary involvement required thoracentesis, and in one, 0.1 per cent Atabrine solution was instilled into the pleural cavity on four occasions.<sup>5</sup> Two cases in which residual nontender hepatic enlargement remained after 30 days of Atabrine therapy were given 10 days of chloroquine therapy combined with Atabrine as an added measure. During this therapy the liver enlargement subsided. Since the intestinal amebic process was healed and the hepatic process presumably healed, the necessity for this is problematic. However, these were United Nations patients whose follow-up was restricted.

## SUMMARY

Clinical data from 15 cases of amebic hepatic abscess are presented. Diagnostic criteria established are:

1. The presence of the clinical syndrome of amebiasis.
2. Demonstration of intestinal lesions by sigmoidoscopic technics, or demonstration of *E. histolytica* in aspirations or stool.
3. Objective evidence of focal hepatic involvement.
4. Unequivocal response to appropriate therapy.

Twelve of the cases complained of sharply localized hepatic pain, and examination disclosed this area to be the area of maximal tenderness. In all cases the pain was sharp and radiated to the back. In six cases the pain also radiated to the clavicle. Enlarged liver and loss of weight were present in all cases. Elevation of the diaphragm was present in 10 cases, and an abdominal mass was palpable in three and demonstrated by x-ray and surgery in one additional case each. All were successfully treated with Atabrine and carbarsone, surgical incision being required in two cases and thoracentesis in two cases. One death occurred from a complicating hepatic carcinoma.

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## TRAUMATIC PARAPLEGIA—RATIONALE OF THERAPY \*

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ONE of the most remarkable paradoxes in the progress of modern medicine has been the appearance of a complex series of problems associated with the care and treatment of the traumatic paraplegic. During and following World War I relatively little thought was given to this category of patients. For one thing, the immediate shock and subsequent overwhelming infection, involving the urinary tract particularly, defied all the therapeutic efforts available to the medical profession at that time, so that the vast majority of casualties rapidly succumbed, leaving but a handful of patients to survive the ravages of their injuries. In time, even this small number became decimated as a result of recurrent infection and intercurrent disease with which we were unable to cope. But perhaps equally unfortunate were those few who, having survived the initial onslaught and subsequent complications, found themselves relegated to an existence rarely more than mere vegetation. Life for the paraplegic—restricted to bed for the most part, plagued by decubiti and other distressing manifestations—presented a dismal outlook, indeed.

With the advent of World War II and the application of a vastly augmented therapeutic armamentarium, a new hope suddenly appeared on the horizon—a hope which brought with it, however, a tremendous challenge to those very forces of advancing medicine responsible for this revelation of encouragement. Improved methods of handling shock, progress in the fields of chemotherapy and, later, antibiotics to combat infection, associated with more efficient casualty evacuation procedures which insured more immediate institution of indicated treatment—these were the factors most intimately concerned with the preservation of life and with the return of paraplegics to the Zone of the Interior in unprecedented numbers.

It has been estimated that by the end of World War II approximately 2,000 paraplegics (including quadriplegics) had survived and had been discharged from the Armed Services to the care of the Veterans Administration. When the magnitude of the problem was realized, it suddenly became clear that this was no new problem, that civilian injuries caused by automobile accidents, industrial accidents and the like were accounting for possibly several times that number of paraplegics throughout the country each year. Thus, while our immediate efforts had been stimulated by and had become devoted to the war casualty, it was readily appreciated that the therapeutic methodologies thereby developed would ultimately apply with

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equal benefit to the present and future paraplegics of our civilian population.

Those of us in the Veterans Administration who first came into contact with the traumatic paraplegics following their recovery from the more immediate effects of their injuries were at once concerned by the dearth of knowledge regarding these disabilities. This lack of understanding was reflected not only by the relatively poor physical condition of the patient as we saw him but by his dejected mental attitude as well. I wish to make it very clear that this is not said in any sense of criticism. Those who labored so diligently to bring these patients through the early critical stages following their injuries performed a most commendable piece of work; moreover, our own unhappy plight with reference to the meager understanding and knowledge of the paraplegic was then little better.

One was particularly impressed by the extreme variation in concept as expressed by the patient himself and as it reflected the thinking of the particular group under whose care he had been prior to his arrival in the Veterans Administration Hospital. At one extreme were those who gravely pictured their life expectancy to be no longer than six months or a year at the most. It was a most difficult task to overcome their manifest discouragement, quite natural under the circumstances, so that they would at least cooperate in the prescribed program of therapy. At the other extreme, and frequently more difficult to cope with, were those paraplegics who, despite irreversible spinal cord damage, came to us with every intention of recovering completely from their disabilities within the space of a few months. This wholly unrealistic attitude required an extremely cautious approach on the part of physicians and other personnel, directed toward a gradual inculcation of understanding and ultimate acceptance by the patient of his disability as a permanent state.

Fortunately, attitudes of this sort are rarely encountered today. Experience has taught us that an early and frank orientation of the patient to the nature and the implications of his disability will obviate the many misunderstandings which so often lead to serious problems in the treatment program. Obviously, individual variations will determine the most desirable approach in each case; consequently, I am firmly convinced that the physician is the only one adequately equipped to undertake the task of orientation—only he will know when the patient is prepared to accept a frank evaluation of his condition, and the manner in which such evaluation can best be presented.

While any semblance of false hope must be meticulously avoided, unless one is absolutely certain that complete transection of the cord has occurred the door should never be closed to the possibility of at least limited recovery of function. Statistics may well show that relatively few cases manifest any real functional return beyond a period of 12 to 18 months following the initial injury; nevertheless, in treating a given paraplegic one should never determine the limits of recovery by the turn of a page on the calendar.



It may be stated that the treatment of the traumatic paraplegic concerns itself with two general phases of medicine: definitive therapy and rehabilitative therapy. In actual practice the problems of both are considered simultaneously, so that the treatment program of one becomes closely integrated with the other in the direction of a common goal. This is extremely important because, with the knowledge that despite his disability he can still have the opportunity to take his place as a self-dependent and productive member of society, there will often be manifest a tremendous improvement in the morale of the paraplegic and he will be much better prepared to cooperate with the staff in the definitive and rehabilitative procedures which have been prescribed.

To this end, our experience has revealed that, wherever possible, one physician should be entrusted with the responsibility for integrating the entire paraplegia treatment program so that it may proceed effectively and decisively in the best interests of the patient. The complex disability of the traumatic paraplegic will usually require the services of physicians representing a number of the specialized fields of medicine, particularly neurology, neurosurgery, plastic surgery, internal medicine, urology, psychiatry, and the field of physical medicine and rehabilitation. Under such circumstances, unless some one physician becomes *the* physician for the patient, the tendency has been for each member of the staff to view the paraplegic as a "case" rather than as an individual, with the interest of each often limited to the particular specialty which he represents. The unfortunate result of the latter method of approach has been that integration of treatment was lost and frequent conflicts ensued, causing delay and confusion in the program of therapy. Moreover, serious complications would occasionally develop with respect to one aspect of the patient's disability while another was being assiduously and forthrightly treated.

But even more significant than the recognition of one physician as the "captain" of the team of personnel concerned with all phases of therapy (and permit me to emphasize the great importance of maintaining the team concept throughout the course of treatment) is the fact that these patients are in such desperate need of a doctor to whom they can come with their many questions and problems and in whom they can place their full confidence.

I am firmly convinced that if we could for one moment place ourselves in the position of the traumatic paraplegic, most of us would have a much more enlightened appreciation of the patient, his problems and his reactions. However, it is no simple matter to fathom the profound impact in all of its ramifications on an individual who at one moment is in complete possession of every one of his faculties and then, within the space of a split second, finds himself bereft of the power to move the lower half of his body (more or less) and deprived of the voluntary control of his urinary, bowel and sexual functions; moreover, the fact that these people suffer no significant injury to their mentality or powers of comprehension only emphasizes the

clarity with which they are able to perceive what they have lost. I mention this to point out the need for deep understanding in the early phases of paraplegia care, when recognition of the full import of the disability must be met with compassion and, at the same time, with judicious realism even in laying the foundation for future planning.

The neurosurgical approach to the treatment of traumatic paraplegia often becomes one of the earliest major considerations following the injury. While in the presence of obvious impingement upon the spinal cord there is, of course, no question of the need for decompression, considering that laminectomy in capable hands is fairly safe, that if carefully performed it should not per se interfere with the future rehabilitation of the paraplegic and, finally, that it may reveal some factor of compression which might otherwise go unrecognized, I feel that this procedure should be given careful consideration in accordance with the indications and in the best interests of the paraplegic.

Anyone who has devoted his time to the care of paraplegics becomes impressed before long with the severe struggle which some patients endure in their attempts to overcome muscle spasm in the affected parts of the body. Varying greatly in intensity from patient to patient, spasm was at times viewed with considerable alarm when it reached a degree of such severity as to interfere seriously with even ordinary nursing care. In some cases the mere touch of the bedcovers would be sufficient to set up terrific reactions of spasm; in other, less severe instances, many of the patient's efforts in the field of physical rehabilitation, particularly ambulation with braces and crutches, were seriously hampered by the spasmodic reactions of involved musculature. I have seen one paraplegic who developed numerous decubiti because severe spasm constantly maintained his body in almost a fetal position; and I have seen ambulating paraplegics thrown completely off balance by sudden spasm in the lower extremities, with serious falls avoided only by the alertness of nearby therapists.

It is interesting to note that, as our knowledge of paraplegia has increased, the need for surgical intervention in the treatment of spasm has diminished. In my opinion, one of the salient reasons for this is the extremely beneficial effect upon spasm of a carefully devised and consistently executed program of physical activity. In some instances, tetanizing electrical currents have been employed in the alleviation of spasm; however, while it is true that by the creation of a state of fatigue in the muscles concerned spasm is thereby eliminated, the effect is but temporary, usually lasting for not more than several hours. Our experience with the use of spasm-relieving drugs in the traumatic paraplegic has thus far left me unimpressed, and I am yet to be convinced of any particular merit which any one of them might have in this regard.

Another neurosurgical procedure which has diminished considerably in incidence is that of chordotomy for the relief of the pain so often experi-

enced by the traumatic paraplegic. This symptom has at times presented a most distressing problem. It is described by some patients as sharp and lancinating in character, by others as burning or crushing, and is referred to the area below the level of the lesion despite the fact that sensation as such may be completely or almost completely absent. While it has been observed that the intensity of this subjective pain usually subsides with the passage of time and under the influence of rehabilitative activities, we know also that a certain element of pain is continually experienced by almost all paraplegics. It is of the utmost importance, therefore, that the patient be made aware of this fact and that he learn to live with this pain, adjusting himself to it by means of such physical and mental activities as will distract and occupy his attention in some constructive manner.

The problem of distinguishing between real pain, which may vary in intensity, and the aggravated manifestations of pain in emotionally unstable patients is at times difficult to resolve. Unfortunately, some physicians have failed to realize the significance of pain in the paraplegic, and I have seen more than one narcotic addiction develop as a result of attempts to relieve this symptom by morphine or other opiates. I do not mean this at all critically—even the physician experienced in paraplegia is frequently hard put to it in his efforts to arrive at a satisfactory solution to the problem—but I do wish to enter a sincere plea for a most cautious approach in considering the treatment of pain in this category of patients.

In viewing the many complex manifestations of the paraplegic, those pertaining to the genitourinary tract are perhaps of greatest concern to the patient. The bilateral lower extremity amputee and the polio victim with extensive paralysis are frequently looked upon with great envy by the paraplegic because the amputee and, generally speaking, the polio patient, have full voluntary control of the functions pertaining to micturition and sexual cohabitation.

Although in the early stages following the injury the problem of the neurogenic bladder may not manifest itself quite so dramatically as an open wound of the spine, considering the future well-being and rehabilitation of the paraplegic the adequate care of each is unquestionably of equal importance.

In the days of World War II and under the pressure of prevailing conditions a cystostomy appeared to be the simplest method of handling the immediate care of the neurogenic bladder. Once accomplished, it required less constant attention than indwelling urethral catheterization—certainly less than any attempts at bladder training—and so the end result seemed to justify that means of insuring bladder drainage. In the light of further experience, many observers in the field of paraplegia have come to view such cystostomy as an emergency procedure, a temporary expedient necessitated by unfavorable conditions and one by which bladder drainage would be assured until the patient could reach an environment more conducive to com-

plete and adequate medical care. This opinion is based not only upon the general undesirability of indefinite cystostomy, or the difficulty of reconciling such method of urinary drainage with a practical realization of total rehabilitation, but also upon the proved fact that most paraplegics can train their bladders to contract reflexly or with a certain element of automaticity.

It should be emphasized that the training of a neurogenic bladder is no simple matter. It requires the conjoint efforts of the patient, the physician and a host of trained technical personnel for many months, during which there can be no relaxation of technic. Not only must each member of the therapeutic team be fully cognizant of his rôle, but the patient must also at all times be aware of the purpose of each step in the process, so that he will understand the importance of his own part in the program and will cooperate fully in striving for the maximal degree of success possible in his individual case. In time, with proper care, most paraplegics can adjust themselves so that they will empty their bladders at stated intervals, such as every three or four hours during the day; and by abstaining from fluids beyond about seven o'clock in the evening many can sleep through the night without being disturbed and without danger of accidental incontinence.

Unfortunately, we are not able invariably to achieve complete success in our bladder training program. Nevertheless, recognizing the fact that there are some bladders which will not respond despite our most diligent efforts, it is even more regrettable to realize that many bladders which could be trained are yet counted amongst our failures because the patient does not maintain the interest or desire to cooperate in the program. In truth, such an attitude is not always the fault of the patient—it may be only a reflection of our own failure to orient him properly in the program and to impress him with its importance.

One of the most disturbing questions posed by the patient, and one which is of grave concern to him, is the question of the effect of his injury upon his sexual powers. Involving as it does tremendous implications with reference to marital relationships and emotional forces, the problem is one of the most difficult with which we have to deal. In this connection, perhaps more than in any other pertaining to the care of the paraplegic, the psychiatrist may find himself called upon to assist in resolving the psychosexual disturbance which may dominate the picture.

Although at the outset of our experience we had our own grave misgivings relative to the recovery of sexual potency in these patients, we have learned that the outlook is not quite so hopeless. While there are as yet no definite criteria by which we may be guided, we know that, despite the absence of sensation, penile erections occur in quite a number of paraplegics and that in many it is adequate for intromission, even though there may be little or no ejaculation. The question of sterility is also one which cannot be readily determined; I am convinced of authenticated cases of paternity, but I am just as thoroughly convinced that in our present state of knowledge we are unable to predict such matters with assurance in any given paraplegic.

In view of the uncertainties presented by this problem, the importance of discussing the subject candidly with the patient cannot be overemphasized. It is also extremely important that the patient's wife, if he is married, or his prospective wife, if he is contemplating marriage, enter into these discussions so that she may become fully aware of the existing potentialities and limitations. Only in this manner can we obviate the painful anxieties and the even more painful frustrations brought about by misinformation and misunderstanding.

Although the loss of voluntary bowel control is considered to be a far less serious menace to the life of the traumatic paraplegic than the dysfunction of his urinary tract, it becomes a matter of some concern to the patient who is striving toward social restoration. In general, it may be stated that the avoidance of dietary indiscretions and the development of a habit, religiously adhering to a fixed hour each day or every other day for this purpose, will usually serve, in time, to establish a certain degree of automaticity in bowel evacuation. At first it will require the use of glycerine suppositories or enemata to empty the bowel, but with unremitting perseverance in the training régime the bowel will ultimately respond in most instances so that the paraplegic may enjoy a reasonable sense of security.

I should like to offer a word of caution at this point. Anyone concerned with the administration of an enema to a paraplegic must never forget that the bowel is also involved in the disturbance of sensory function found elsewhere below the level of the lesion. Unless an exceptional degree of care is exercised it is possible to cause serious damage to the bowel, even perforation, without any immediate reaction on the part of the patient to indicate that any harm has been done. This is mentioned particularly because, until the individual has learned to take his own enema, its administration is often left to a hospital attendant or aide, who should therefore be thoroughly oriented to the requirements of the occasion. While there is a similar sensory disturbance in the urinary tract, major instrumentation is of course performed by the physician, who is well aware of the inherent dangers to be guarded against; where catheterization or other procedures are performed by technical personnel, thorough orientation and training are extremely essential if serious accidents are to be avoided.

The concept of the rôle of the psychiatrist in the treatment of traumatic paraplegia has been altered considerably since the early days of our experience. I firmly believe that the behavior of those groups of paraplegics who first came to our attention influenced many of us to conclude that a psychiatric problem existed and was of major consequence in most of these patients. However, as we learned more about the disability and its ramifications we began to realize that in almost all instances we were dealing with bad habits rather than with psychiatric disorders.

As I have said before, the psychosexual field is one of the more significant areas within which the help of the psychiatrist may become of paramount



importance. Another problem encountered from time to time involves those paraplegics who, because of a lack of insight into the significance of their disabilities, their limitations and their capabilities, flounder about aimlessly, unable to appreciate and take full advantage of available rehabilitation facilities. It should be noted that paraplegics are often loath to receive assistance from the psychiatrist, fearing a possible stigma relating to their mentality. It is essential, therefore, that this matter be carefully broached to the patient, for without his full cooperation there can be little hope of success.

At times it may be possible to apply the principles of group psychotherapy, as determined by the psychiatrist. In this respect, trained psychologists are often able to serve a very useful purpose in assisting the psychiatrist with such group therapy, and under appropriate circumstances may even conduct the group sessions independently. It should be pointed out that while the psychologist has much to offer to this category of patients, his activity should at least come under the general supervision of the psychiatrist to insure the proper conduct of the program.

One of the most elusive problems in the early months of our experience with the traumatic paraplegic was that concerned with the care and treatment of decubiti. The early use of plaster casts, infrequent changes in position, undue exposure to urine-soaked linens, poor nutrition—these and many other factors contributed to a most appalling incidence of pressure sores in these patients. Our first measures were naturally directed toward an elimination of those factors which favored the development of ulcers. Meticulous attention was given to every phase of nursing care, and a program was instituted whereby the patient was turned every two hours while he remained bedfast. The Stryker bed frame came into very active use in this respect because it permitted the patient to be turned with much greater ease. The paraplegic in the wheel chair soon learned the importance of shifting about to avoid pressure on any one area for too long a time, and when he was able to stand up in braces he had even greater opportunity to relieve excessive ischial pressure.

Because many of the early plastic surgical operations were unsuccessful and recurrences were frequent, numerous attempts were made to encourage spontaneous closure of existing ulcers. However, it was soon apparent that conservative measures were of little value except in the very small ulcers; when the ulcer was of significant size not only did it require an exorbitant length of time to heal, thereby considerably delaying the rehabilitation program, but the resultant scar was paper thin and brittle, breaking down upon the slightest provocation.

With respect to the institution of any plastic surgery, it must be recognized that, unless the patient's nutritional requirements have first been adequately met, the surgical procedure may well be doomed to ultimate failure. This often presents a very serious problem because the existing malnutrition is frequently associated with anorexia and may become further



aggravated by the constant loss of protein substance in the serous exudation from the decubitus. Hence, experience has revealed the need for a daily intake of approximately 200 gm. of protein to meet the body requirements of the paraplegic and to replace losses from exuding ulcers; if necessary, parenteral supplements must be utilized to make up for deficiencies in oral intake.

In consideration of the sensory impairment of involved skin surfaces, the paraplegic must be constantly on his guard lest he inadvertently expose himself to external traumata which may cause serious injury to the tissues. I have had occasion to observe the almost incredible rapidity with which an ulcer can develop in these patients. A cigarette burn, a brief encounter with a hot radiator in a room, and within 24 hours there are the unmistakable manifestations of ulcer formation. It is very important, therefore, that all exposed hot water pipes, steam pipes and radiators be relocated or adequately covered, that proper thermostatic control valves be installed in shower units, and that every appliance or piece of equipment with which the patient comes into contact be closely scrutinized to obviate any possible source of pressure, abrasion or other injury. The paraplegic himself, as well as his attendants, should be enjoined to examine the involved skin surfaces carefully and frequently—at the end of each day, if possible—so that any suspicious looking areas may receive immediate attention, including the determination of causative factors.

Whenever I see a paraplegic ambulating with his braces I am extremely grateful for our present day enlightenment in the bracing of these patients. Those who remember the formidable array of hardware with which we burdened our early paraplegics will surely appreciate the significance of this statement. It was little wonder that many paraplegics preferred to remain in bed rather than to encase themselves in the "suits of armor" which had been fabricated for them. Of course, the need for bracing will at all times depend upon the level of the lesion, the degree of spinal cord damage and, in the final analysis, the purpose to be achieved in the individual case, which is usually to provide some functional assistance. Consequently, no brace is ever prescribed unless it will serve to further the interests of the particular patient for whom it is constructed.

In brief, most paraplegics have little more than two long leg braces—even the pelvic band which was formerly part of almost every paraplegic's stock of appliances has now been discarded in many cases. Furthermore, should recovery of function make either long leg brace unnecessary, it is promptly replaced by a more appropriate appliance, our aim being always to use the minimal amount of bracing required by the patient.

In view of the prolonged period of time often required for the fabrication of appliances, various devices such as boards or tilt tables with straps have been utilized to hold the patient firmly, so that he can be placed in the upright position for varying periods of time each day while awaiting the com-

pletion of his braces. These devices are also used at times to place quadriplegics in the upright position even though leg bracing, as such, may not be indicated for them since, in the absence of adequate motor control of the upper extremities, it would serve no useful purpose. Great care should be exercised when such patients are brought to the upright position, since postural hypotension may ensue and cause sudden syncope.

Occasionally a partial quadriplegic with not too much loss of voluntary power in the upper extremities may be permitted to attempt ambulation with braces and crutches. However, this should be approached with a great deal of caution, for obvious reasons—the hurt of a fall may not be nearly so painful as the experience of frustration.

The responsibility of the physician should not cease merely with the prescription for necessary bracing. It is equally his responsibility to assure himself that the completed braces will, in fact, accomplish the purpose for which they were constructed. An ill-fitting brace may be worse than no brace at all, and in the paraplegic it may be particularly injurious.

The Physical Medicine and Rehabilitation Service becomes concerned with the traumatic paraplegic almost from the very day he enters the hospital, and its concern continues until the day he leaves. Aside from the physicomical measures applied in the treatment of some of the more specific manifestations of the disability, such as ultraviolet irradiation for decubiti, the early interest of the physiatrist lies in the realm of physical reconditioning. While this may be of a general nature at first, in time it will become directed toward the future prospects for each individual patient. For the paraplegic with adequate motor control in his upper extremities, this will generally take the form of preambulation activities. Even while in bed, the patient should pursue the prescribed exercises as vigorously as possible. The road to final ambulation with braces and crutches is a long one, and there are often many unavoidable interruptions by reason of surgical procedures or other causes; consequently, it becomes necessary to take full advantage of every possible opportunity to proceed with and to further the physical efforts of the patient.

As soon as the condition of the paraplegic permits, he should be brought to the clinic for his treatment. Aside from other factors involved, it is psychologically sound to wean the patient from his bed and from the ward atmosphere at the earliest possible moment. Here again a purpose is served, in that the paraplegic is able to see others with disabilities similar to his own but in more advanced stages of therapy—nothing can do so much for the morale of a paraplegic as the sight of other paraplegics actually performing those activities toward which he himself is so assiduously striving.

With the use of the wheelchair introduced, the paraplegic is taught how to move himself from bed to wheelchair and how to take care of his daily

toilet and other needs without assistance. When his braces are received and approved by the physician he must learn how to put them on and take them off by himself, in consonance with the prevailing motif of self-dependence.

The question of ambulation for the paraplegic with braces and crutches has been reviewed many times since our original concepts were first established. To begin with, one must understand the tremendous physical exertion required for such ambulation. To be sure, we have all, on occasion, seen the acrobatic type of paraplegic who can perform most difficult feats with unusual ease; however, most paraplegics, despite the extensive régime of exercise preparatory to and in conjunction with ambulation, find it extremely tiring to ambulate for any prolonged period of time.

In retrospect, our original aspirations were far from realistic, and many paraplegics rebelled at prolonged ambulation or ascending and descending too many steps, including a very high step which had been carefully constructed to simulate the entrance to a bus. Ultimately we had to concede that most paraplegics were going to accomplish the greater part of their "ambulation" right in their own wheelchairs, and so we gradually diminished the intensity of our program. A further circumstance was the fact that many of our paraplegics were receiving and operating motor cars with hand controls, and so the need for training that they might avail themselves of public transportation became relatively unimportant.

It is generally agreed, however, that every paraplegic should be trained as far as possible in the essentials of ambulation with braces and crutches. This training will unquestionably permit the individual a much greater degree of freedom in his daily life. The exact type of crutch gait is not too important in most instances. While a swing-through gait permits more rapid progress, it is more difficult to achieve and is limited, of course, to open, unobstructed areas. Most frequently, the swing-to gait, together with simple side stepping and backward stepping gaits, will suffice to satisfy the usual requirements of the traumatic paraplegic.

Of considerable significance to the paraplegic are the many physiologic advantages associated with ambulation on crutches and braces. One of the most important effects of such ambulation is reflected in the density of the long bones of the lower extremities. The individual who persists in confining himself to his wheelchair will present a picture of extensive osteoporosis in those bones; as a consequence, I have observed several pathologic fractures following minor traumata—one patient suffered fractures of his tibia and fibula when he happened to strike his leg against the door of his car. With ambulation, the longitudinal pressure upon the long bones of the extremities serves to stimulate calcification, thereby obviating the dangers of osteoporosis and minimizing calculosis in the urinary tract and in other areas of the body. Another important advantage of crutch and

brace ambulation is the relief from prolonged pressure upon the buttocks, thereby eliminating a cogent factor in the causation of decubiti.

A word should be said in passing about a recommendation of which we hear but little today. At one time it was thought by some few that since the complete paraplegic had lost all motor and sensory power in both lower extremities, he would be much better off without those limbs, and so they recommended bilateral amputation. It is indeed most fortunate that only rarely was this actually accomplished. I have seen one or two such cases who had undergone bilateral amputations before they came to us, and I am more than ever convinced that amputation of the paralyzed limbs should under no circumstances be lightly undertaken. There is something about the retention of the body image which means a great deal to the individual, even to the paraplegic whose wasted extremities may, in truth, be no more than so much "dead wood" to him.

For the quadriplegic with significant impairment of motor power in the upper extremities there is no ambulation program which can be undertaken with any degree of practicability or safety. However, our problem here is to develop the residual function in the upper extremities to permit the accomplishment of as many self-care activities as possible. In this respect, many ingenious devices have been developed and many weeks of painstaking effort have gone into the program, which at times may have had such "simple" goals for the patient as feeding or shaving himself or brushing his own teeth. Yet it has often been truly amazing and gratifying to perceive the achievements which could be attained with the help of strong motivation and perseverance.

There can be no doubt of the fact that it is basically and physiologically unsound for the paraplegic, particularly the younger paraplegic, merely to sit back and let the world pass by. In keeping with this line of reasoning we have bent every effort to assist the traumatic paraplegic in the choice of some vocational objective commensurate with his capabilities and within the limits of his disabilities. As soon as the physician feels that the patient is in condition to discuss such matters, the vocational counselor should initiate preliminary discussions which may set the stage for future planning. Of course, before such planning will actually begin to take shape a great deal more will be required, such as a Social Service survey; psychological, aptitude and interest tests; perhaps even a more practical approach within simulated classroom, office or workshop conditions, under the supervision of the physiatrist. Last, but not least, there must be a reasonable assurance that the ultimate plan will be realistic from every point of view, including that of anticipated employability of services or products, as the case might be. Unless the vocational objective, whatever it might be, can find some practical application and use, the resultant discouragement and frustration may well defeat the entire purpose of the rehabilitation program.

In arriving at any final decisions regarding vocational planning, we have often found the conference table to be extremely advantageous. With all staff members concerned available to discuss the problems at hand, and with the patient also available to participate in pertinent phases of the discussion, the entire program can be more effectively integrated and the patient's cooperation more readily secured. I wish to emphasize this latter point because, as I have often said of any rehabilitation program, we can advise and guide, but it is the patient who does most of the work; hence, unless his full cooperation is secured, the program of rehabilitation will have little opportunity for success.

The question of education and training of the paraplegic following his discharge from the hospital often arises. For the individual who has entitlement under existing legislation granting veteran benefits, the problem may be readily resolved. However, where such benefits do not exist or are not adequate for the purpose, it may become necessary to enlist the aid of State Rehabilitation Agencies or other community resources. In this respect, we must avoid a tendency which I have found to exist on numerous occasions: too often a tremendous amount of well directed time, energy and enthusiasm on the part of both patient and personnel has gone for naught because, when the patient was discharged from the hospital, there was no one to pick up the thread of planning and the recommendations which had been so carefully prepared, or to insure that such planning and recommendations would proceed to some final goal of successful achievement. It should be emphasized that this has not been the fault of any one individual or group, but rather represents a lack of adequate liaison among interested agencies within the community which would, in practice, serve to obviate this loss of continuity in rehabilitation planning. There is yet much to be done in this regard, for while it may be a credit to the medical profession to be able to outline with reasonable accuracy the essential ingredients of a prescription, unless that prescription can be filled with the same degree of care and accuracy the ultimate interests of the patient will not be served. I feel, however, that having come thus far, we shall in time correct this deficiency and extend to every paraplegic the offer of a rehabilitation program complete in every respect.

At this time I should like to present some statistical information compiled by the Medical Statistics Division of the Veterans Administration which may be of interest.

A study covering the period between January 1, 1946, and September 30, 1951, showed that 3,663 cases of traumatic paraplegia (including 531 quadriplegics) were treated in the Veterans Administration Hospital system. Of this number, 182 were admitted prior to January 1, 1946.

The distribution of these patients in terms of the level of their lesions is as follows:

Level of Lesion	Number of Patients
Cervical	
C-1	8
C-2	10
C-3	23
C-4	59
C-5	185
C-6	212
C-7	104
C-Exact level not clearly stated	38
Total Cervical	639
Dorsal	
D-1	40
D-2	74
D-3	89
D-4	167
D-5	154
D-6	161
D-7	152
D-8	173
D-9	155
D-10	234
D-11	288
D-12	372
D-Exact level not clearly stated	14
Total Dorsal	2,073
Lumbar	
L-1	346
L-2	124
L-3	88
L-4	63
L-5	40
L-Exact level not clearly stated	16
Total Lumbar	677
Sacral	
S-1	9
S-2	6
S-3	5
S-4	1
S-Exact level not clearly stated	2
Total Sacral	23
Level of Lesion Not Clearly Stated	251
Total Traumatic Cases	3,663

The following table shows the length of hospital stay during the *initial* admission, computed as of September 30, 1951:

Length of Hospitalization	Number of Patients
Up to 6 months	1,665
6 months-1 year	692
1-2 years	588
2-3 years	316
3-4 years	179
4 years or longer	223
Total	3,663



Of the 223 patients hospitalized for a period of four years or longer, 53 were quadriplegics, representing 10 per cent of their original number (531), whereas the remainder represent only about 5.5 per cent of those with involvement restricted to the lower extremities. This is quite understandable, since the quadriplegic is less amenable to home care and hence to discharge from the hospital. The reasons for prolonged hospitalization in the cases of paraplegics with full use of their upper extremities are varied and at times obscure. A number of these patients represent true medical problems: recurring or nonhealing decubiti, old contractures of the lower extremities acquired during the early months following their injury and presenting difficulties in correction, persisting urologic problems, etc. However, some paraplegics have developed so great a fear of returning to their homes and to society that even when they leave the hospital on pass for several days they are extremely uncomfortable and unhappy until they return to the ward.

Within the last mentioned group, as well as among those whose problems are not so tangible, we will often find many of our rehabilitation failures. These paraplegics have never been able to develop sufficient motivation to utilize their residual abilities and potentialities to the maximal degree. They are often referred to as non-rehabilitatable—and yet I sometimes wonder how far they actually represent our own inadequacies. Perhaps some day we may learn new methods of approach, or learn how to improve the effectiveness of our present methods so that some of these men may yet be salvaged. However, of one thing I am certain: Our efforts must continue unabated, for if these men are to be rehabilitated at all it must be done soon, while they are yet young—each year that passes will increase and compound the difficulties.

A compilation of hospital readmissions of the patients making up this study disclosed a total of 4,039 such re-admissions, of which 48 occurred prior to January 1, 1946. The following table shows the length of time the patients remained when rehospitalization became necessary:

Length of Rehospitalization	Number of Re-admissions
1-10 days	1,098
11-30 days	939
1-6 months	1,406
6-12 months	345
1-2 years	173
2-3 years	51
3-4 years	21
4 years or longer	6
Total	4,039

The large number of paraplegics rehospitalized for only one to 10 days consists almost entirely of patients called in for recheck examinations and studies. (In evaluating the figures in this table it should be remembered that they represent numbers of re-admissions and not numbers of separate patients; a given patient may have been re-admitted more than once during the course of time covered by the study.) The fact that more than half of

the total number of re-admissions were for a period of 30 days or less signifies that, aside from recheck examination, many of these patients came in for the treatment of minor conditions, such as urologic flare-ups, etc., which responded to therapy within a short time.

The 1,406 re-admissions for periods of one to six months obviously represent instances where the treatment was of a more complex nature, such as plastic repair of a decubital ulcer, etc. However, when we realize that over 85 per cent of re-admissions did not extend beyond six months we are struck by a significant thought: Once a paraplegic has reached the point where he is ready for and agreeable to discharge from the hospital, if it ever becomes necessary for him to be rehospitalized for one reason or another he is almost always extremely eager to complete his treatment and return home. This has been forcibly brought to our attention time and again. It is even more significant to note that many paraplegics who strongly resisted discharge from their initial hospitalization, having subsequently adjusted to living outside the hospital, become just as desirous of leaving at the earliest possible date following any required future re-admission.

As to the relationship of paraplegia and its associated disabilities to the need for rehospitalization, of the 4,039 instances above recorded, only 227 cases required re-admission as a result of unrelated causes, presumably intercurrent disease, etc. In 27 cases the relationship was not clearly stated.

In conjunction with the above statistical study, there was also undertaken a review of the death rates among the 2,949 traumatic paraplegics (including quadriplegics) who were admitted to the Veterans Administration Hospital System between January 1, 1946, and December 31, 1950. The following table shows the number of deaths occurring each year and their relationship to the duration of exposure:

Year of Admission	Total Admissions	Total Deaths	Deaths within Specified Years of Exposure				
			1 Yr.	2 Yrs.	3 Yrs.	4 Yrs.	5 Yrs.
1946	1,240	102	24	25	22	19	12
1947	481	31	15	6	7	3	X
1948	442	46	25	8	13	X	X
1949	391	24	18	6	X	X	X
1950	395	23	23	X	X	X	X
Totals	2,949	226	105	45	42	22	12

The relatively small number of cases involved in this study, coupled with the relatively short period of time during which these patients have been under our observation, does not permit us to draw any definite conclusions from these figures. However, certain trends do appear to be significant. Aside from the figures for the 1946 group of admissions, all others show a considerable drop in mortality following the first year of exposure. The nonconformity to this trend on the part of the 1946 group is actually more

apparent than real, for during that year the Veterans Administration took over from the Armed Services Hospitals large numbers of paraplegics, most of whom had already been hospitalized for some years. Thus it would appear that following the first year of his disability the paraplegic, having come through the initial period of spinal shock, should have a better opportunity for survival.

While there are no available data on the immediate causes of death in the cases above reported, from personal observations and discussions with others in the field I have been impressed by the frequency with which renal insufficiency has appeared as a precursor to death in the paraplegic. Considering the nature of the disability, this is of course not at all surprising. Studies in the field of pathology are bringing to light other interesting factors, such as extensive amyloidosis, which we might also have anticipated, considering the course of events in the life of the paraplegic, punctuated as it sometimes is by recurrent bouts of infection, malnutrition, etc.

The over-all death rate of little more than 7.5 per cent, as reflected in the above figures, cannot be accepted without certain known reservations. First of all, many of our paraplegics have come to us from Armed Services Hospitals, and some who sustained their injuries in civilian life have been transferred from civilian hospitals, but in either case it must be remembered that these patients represented the survivors not only of the acute onslaught but also of variable periods following the immediate injury. Second, considering the relatively large number of paraplegics among the non-veteran population, some correlation with the latter experience will also become necessary before we can properly evaluate our own findings.

It is felt that this discussion would not be complete without a few words about the future. The field of research is becoming more and more concerned with the problem of injury to the spinal cord. Of course, the ideal approach, looking to regeneration of the injured portion of the human cord and extending distally with more or less complete restoration of function, is indeed far from being realized. The thought of a graft to bridge effectively the gap of destruction in the cords of paraplegics is yet little more than a gleam in the eye of the neurosurgeon.

However, in various laboratories animal experimentation is going on involving the induction of spinal cord injuries followed by varying therapeutic efforts, including transplantation of spinal cord roots to afford communication with nerve elements below the level of injury, etc. In conjunction with some of this work, a pyrogenic polysaccharide of bacterial origin has reportedly enhanced spinal cord regeneration by obviating the formation of a firm impenetrable scar at the site of cord injury and, instead, causing a soft matrix to form through which regenerating cord fibers could pass with relative ease.

The work that has been done thus far is fascinating; however, it is necessary to simulate more closely the types of spinal cord injuries which come to our attention in actual practice. There is obviously a tremendous

difference between the clean cut of a spinal cord under the controlled aseptic conditions of the laboratory and the destructive lesion which is caused by a bullet, a piece of shrapnel or a crushing impact sustained in an automobile accident or a mining accident. This observation is interjected not to minimize the value of what has been done, but merely to emphasize the need for caution in the evaluation and application of our present laboratory findings. In this respect, I wish to voice most strenuously a plea for extreme circumspection before permitting any report of therapy to reach the lay public, and more particularly the paraplegics themselves. It has always been my contention that conclusions based upon insufficient data are of undetermined value; to display any unwarranted enthusiasm which might thereby raise false hope for recovery in the minds of these severely disabled individuals is, in my opinion, an act of unmitigated cruelty. Nevertheless, I feel just as strongly that, for the very reason that we are dealing with so serious a disability, no therapeutic measure should ever be lightly discarded, irrespective of how remote the possibility for its success might appear to be.

From the standpoint of the clinician, until such time as some new drug or therapeutic procedure shall dramatically change the present course of events, the indications are clearly along the lines of close observation of existing technic, with such modification as will be dictated by the careful evaluation of a growing experience. There is much to be done in this relatively young field—and not the least of our problems lie in the field of rehabilitation. The extent to which our communities may take on their share of responsibility in the total rehabilitation of the traumatic paraplegic has not yet been fully explored, but I am convinced that therein lie great possibilities. To borrow a thought from Doctor Rusk, we must not forget that, having added years to the lives of the traumatic paraplegics, we must now, above all, add life to their years.

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## ATELECTASIS IN UPPER RESPIRATORY INFECTIONS IN POST-TRAUMATIC PARALYZED PATIENTS\*

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PULMONARY atelectasis in post-traumatic paralyzed patients, more frequently quadriplegics than paraplegics, occurs not uncommonly during an upper respiratory infection. However, a discussion of this topic was not found in a review of the available medical literature.

Atelectasis which occurs in postoperative cases and in poliomyelitis has been rather frequently described. Morrow and Stimson<sup>2</sup> described four cases of atelectasis in poliomyelitis and many similar instances have been observed. Jacobson et al.,<sup>1</sup> in a recent paper on pulmonary complications in acute bulbar poliomyelitis, observe that atelectasis is the most frequent and most fatal complication.

This hospital has a cord injury service of 175 beds. The census of quadriplegic patients is generally 50. In the past six months, four cases of atelectasis in these paralyzed patients during an upper respiratory infection have been studied, and their histories form the basis of this report.

### CASE REPORTS

*Case 1.* A 28 year old male became quadriplegic due to an anterior dislocation of the fourth cervical vertebra on the fifth. The dislocation occurred in an automobile accident in April, 1952.

The patient complained of a cold with copious expectoration eight months after injury. His temperature was elevated to 102° F. and the white blood count revealed a leukocytosis of 30,000, with 91 per cent polymorphonuclear cells. X-ray examination of the chest (figure 1a) two days later revealed an atelectasis of the left lung, with deviation of the heart and mediastinum to the left. A chest film in expiration (figure 1b) revealed a shift of the heart and mediastinum to normal position, with no evidence of infiltration in the lungs. Following the institution of appropriate therapy the patient recovered clinically and was not rechecked radiologically. However, subsequent routine periodic chest x-ray examinations were normal.

*Case 2.* A 21 year old male became quadriplegic below the level of the fifth cervical vertebra on July 20, 1952, the result of diving into shallow water.

Six months later, while still in the hospital, he developed an upper respiratory infection with thick greenish sputum and cough. His temperature and white blood count were normal.

X-ray examination (figure 2a) showed an atelectasis of the right lung, with deviation of the heart to the right, elevation of the diaphragm and narrowing of the

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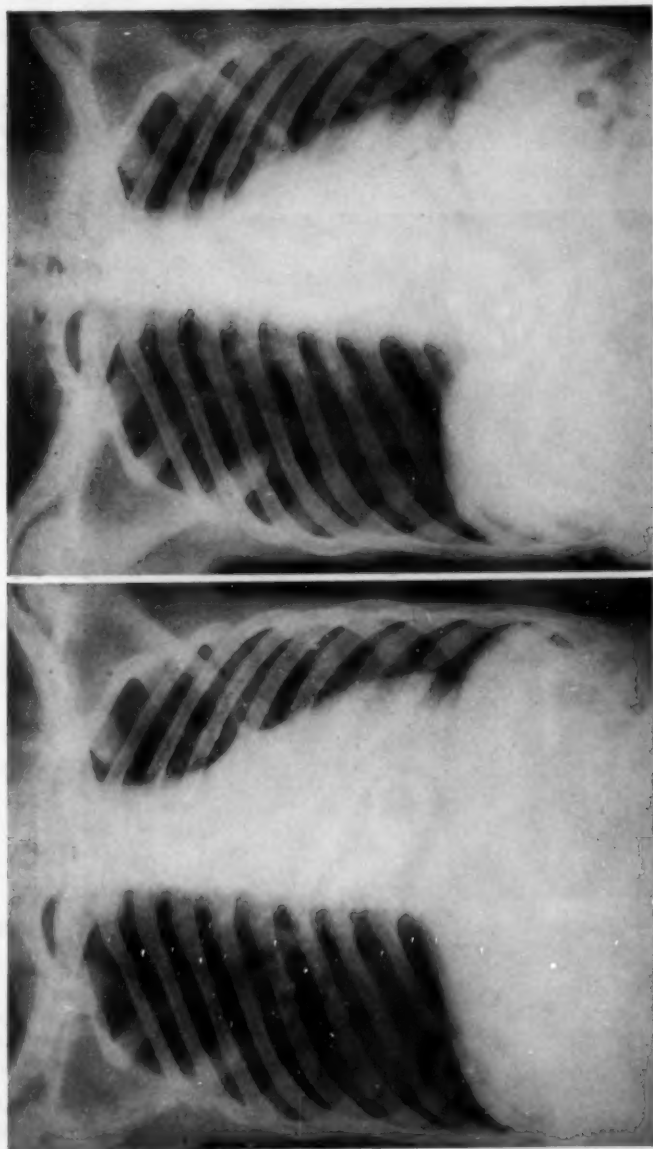


FIG. 1a. Chest x-ray examination. Deviation of the heart to the left, narrowing of the left intercostal spaces and slight elevation of the left diaphragm indicate atelectasis of the left lung. b. Expiration film reveals the shift of the heart to normal position, but the narrowed left intercostal spaces and slightly elevated left diaphragm remain unchanged.

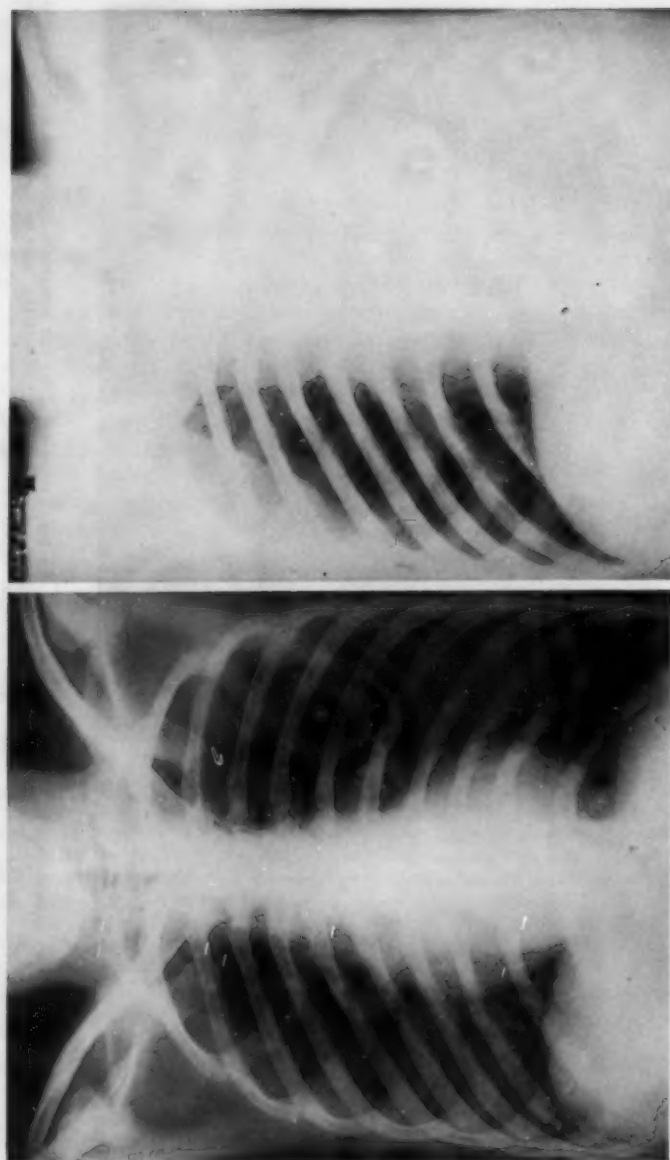


FIG. 2a. Chest x-ray examination demonstrates slight shift of the heart to the right, narrowing of the right intercostal spaces and elevation of the right diaphragm consistent with right pulmonary atelectasis. *b*. Four days later, atelectasis of the left lung.

right intercostal spaces. Active therapy was started immediately, and reexamination of the chest (figure 2b) four days later demonstrated re-aeration of the right lung. However, atelectasis of the left lung was noted.

Two days later, check-up x-ray of the chest (figure 2c) revealed normal findings.

*Case 3.* A 38 year old male paraplegic patient with a seventh dorsal vertebral level as a result of an automobile accident in January, 1951, was re-admitted for routine check-up 27 months later. He complained of left chest pain. His temperature was 101° F. and became normal 12 hours later. The white blood count was normal.

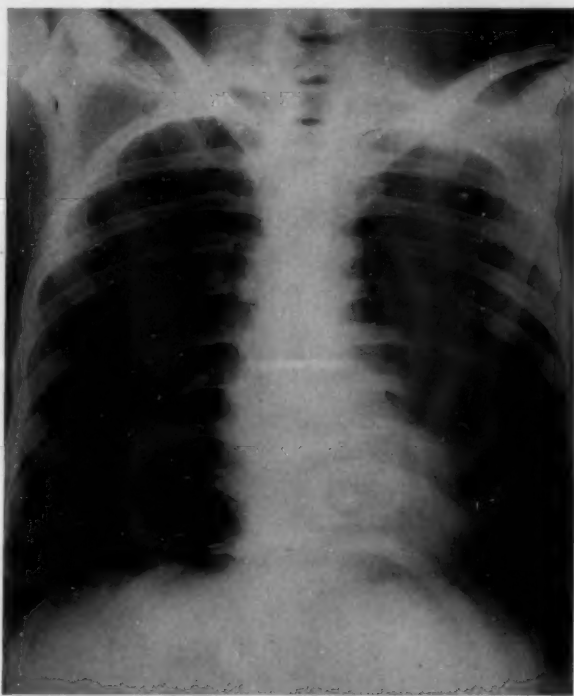


FIG. 2c. Reexamination two days later reveals normal aeration of the lung fields and the normal position of the heart and diaphragms.

Chest x-ray examination (figure 3a) revealed a slight deviation of the heart to the left, slight narrowing of the intercostal spaces and elevation of the left diaphragm indicative of atelectasis. Therapy was started, and roentgen recheck of the chest (figure 3b) three days later demonstrated no abnormality.

*Case 4.* A 27 year old male became quadriplegic September, 1946, below the level of the sixth cervical vertebra as a result of a dive into shallow water. Six and a half years later he was re-admitted with the complaints of headache, fever, chills, cough and chest pains of 48 hours' duration. The cough was productive of thick greenish yellow sputum.

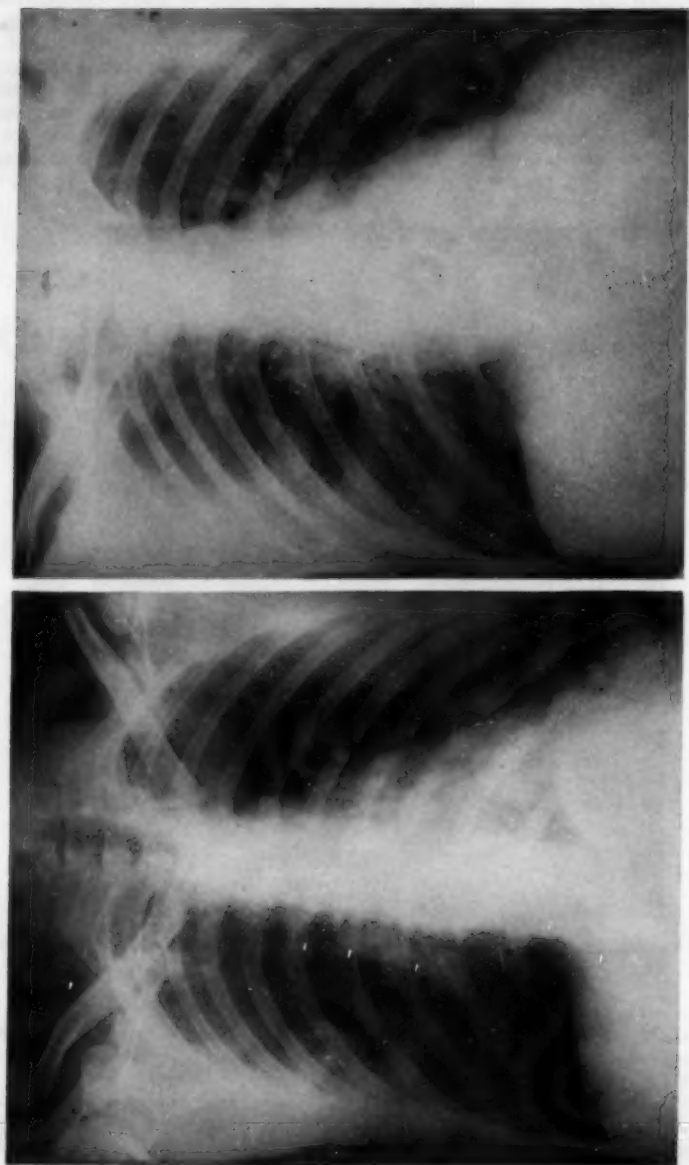


FIG. 3a. Roentgen chest study demonstrates left pulmonary atelectasis. *b*. Restudy three days later demonstrates a normal chest x-ray except for slight elevation of the left diaphragm.

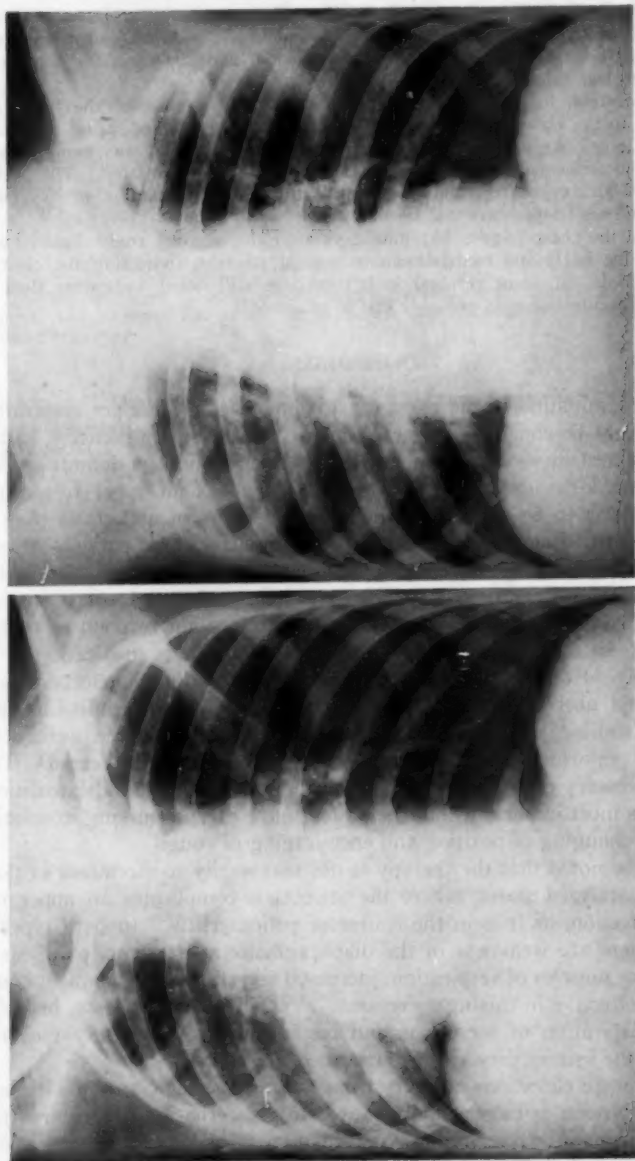


FIG. 4a. X-ray examination of the chest reveals a right pulmonary atelectasis and infiltration of the right midlung field, probably due to pneumonia. b. Repeat chest x-ray examination three days later demonstrates re-aeration of the right lung atelectasis and resolving right pneumonic process.

Physical examination revealed an inspiratory lag on the right. Posteriorly and laterally there were dullness, diminished breath sounds and some medium moist râles. The temperature was 103° F. The white blood count was 20,000, with 86 per cent polymorphonuclear cells.

Chest roentgen findings (figure 4a) demonstrated the shift of the heart and mediastinum to the right and elevation of the right diaphragm indicating atelectasis of the right lung. An area of density in the right midlung field was thought to be due entirely to atelectasis, but a pneumonia could not be differentiated. The patient was placed in an oxygen tent and given active therapy. He was out of oxygen in three days and his temperature was normal in one week.

X-ray of the chest (figure 4b) four days after the original study demonstrated the shift of the heart and mediastinum to normal position, indicating the clearing of the atelectasis, but some residual infiltration was still noted, indicating that the midlung field infiltration was probably due to pneumonia.

### DISCUSSION

X-ray examination of the chest for a common cold or upper respiratory infection might be considered overzealous care in medical practice. But in paralyzed states, in view of the preceding histories, there is definite indication for chest x-ray examination at the first signs of an upper respiratory infection. It is to be noted that the roentgen signs of atelectasis may be minimal and the diagnosis has to be kept in mind. These patients, due to their condition, usually have had previous x-rays, and the comparison studies make the diagnosis of atelectasis more readily apparent. Further, follow-up studies seem advisable if the infection does not respond to routine therapy, for, in the presence of atelectasis, more adequate medication is indicated to avoid the further complications of infection and atelectasis such as pneumonia, abscess formation and fibrosis. The therapy routine in these cases was similar and effective. This consisted of adequate antibiotics, ammonium chloride, aminophylline, and oxygen when indicated. This last was necessary only in the fourth case. Along with the indicated medications, it is most important that the patient have careful nursing, consisting of frequent changing of position and encouraging of cough.

It is to be noted that the therapy is not necessarily so strenuous in post-traumatic paralyzed states, where the atelectasis complicates an upper respiratory infection, as it is in the course of poliomyelitis. In both types of paralysis there are weakness of the diaphragmatic movements, paralysis of the accessory muscles of respiration, increased secretions, and frequent cough which is ineffective in raising secretions. Yet, in the latter cases, bronchoscopy for aspiration of secretions and respirators are frequently required, whereas in the former they are rarely needed.

Temperature elevations are very common in paraplegic and quadriplegic patients. Pyrexia is most usually caused by exacerbation of urinary tract infection, which is ever present, and formation of decubitus ulcerations. But, in the presence of an upper respiratory infection atelectasis as a cause of the temperature rise must be considered. It can be readily demonstrated



by x-ray examination, and the other causes of fever in post-traumatic paralyzed states can be readily differentiated.

#### SUMMARY

1. Four cases of atelectasis occurring in the course of an upper respiratory infection in post-traumatic paralyzed patients have been reported, and the value of chest x-ray examination has been stressed.

2. The essentials of effective therapy in these cases have been outlined.

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## DIFFERENTIAL DIAGNOSIS OF "REGURGITATION" JAUNDICE: THE RÔLE OF NEEDLE LIVER BIOPSY \*

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IN the course of the last six years 529 needle biopsies of the liver were performed in this hospital. Somewhat less than one half of these biopsies were obtained from patients with jaundice. The procedure was carried out with the Vim-Silverman needle. There were no fatalities. However, serious complications arose in two patients: post-puncture hemorrhage from the liver in one, and biliary peritonitis in the other, necessitating surgical intervention in both instances.

It is not the purpose of this article to present a statistical analysis of this material, as such will be done at another time. Rather, it is intended to show by means of the illustrative cases how liver biopsy may profitably supplement other data usually considered in the differential diagnosis of jaundice. On the other hand, it is not intended here to orient the problem solely in the direction of this particular laboratory procedure. Instead, the whole subject of the differential diagnosis of jaundice will be briefly reviewed in some of its salient features, with the liver biopsy as only one aspect of the case.

There are few diagnostic problems more baffling than those which sometimes arise in dealing with icteric patients. Nevertheless, in most instances the cause of icterus can be determined without any great difficulty. In many cases the diagnosis can be made on the basis of history and physical findings alone.

However, as important as historical data are, they may be misleading. A 20 year old youth with jaundice probably has infectious hepatitis, and a man of 60, a malignant obstruction. On the other hand, the youth may turn out to have calculous obstruction and the 60 year old man, a homologous serum hepatitis. The patient may have been exposed to some hepatotoxic agent but have jaundice on an entirely different basis. *Total* anorexia is characteristically one of the prodromal symptoms of infectious hepatitis, but we have seen it in an occasional patient with carcinoma of the pancreas, developing some weeks before the advent of pain or jaundice. Pruritus is equally characteristic of extrahepatic biliary obstruction caused by carcinoma and hepatogenous jaundice with obstructive features; in both circumstances pruritus may precede the onset of icterus by days, weeks or even months. We usually think of gallstones as a painful disease, but a common duct stone may give rise to painless jaundice, particularly in older

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people. To complicate matters still further, in the latter case associated cholangitis with multiple liver abscesses may result in a picture of severe sepsis, distracting one's attention from the underlying obstructive factor. To the great surprise of all concerned, the jaundiced patient with biliary colic, strongly suggesting a common duct stone, may turn out to have a malignancy of the bile ducts. The physical findings may be equally misleading. An enlarged liver may indicate primary hepatic disease in one patient, and secondary "hydrohepatosis" in another. Fotor hepaticus is a bedside test of hepatic insufficiency, but not necessarily of primary hepatic failure. A spider angioma will prove to be a "red herring" in a patient who actually has a common duct neoplasm. A large and exquisitely tender liver does not always harbor only an inflammatory process: it may be a carcinoma. Examples of this sort can be multiplied ad infinitum.

Thus, whereas in most patients a carefully taken history and a painstakingly conducted physical examination will establish the cause of jaundice, in a few, laboratory tests must also be performed before one can arrive at a satisfactory solution of the problem at hand.

The intelligent application and the proper evaluation of such laboratory tests are predicated upon some degree of familiarity with the fundamental features of pathologic physiology. The mechanism and classification of jaundice postulated by Rich<sup>1</sup> are still valid, at least for practical purposes, with only comparatively minor modifications. Thus the "retention" type of jaundice will result from overproduction of bilirubin in the hemolytic anemias, or when a constitutional hepatic dysfunction exists, characterized by an increased threshold of the hepatic cells to the excretion of bilirubin produced in normal amounts (rare familial nonhemolytic icterus). Presumably, so effective is the normal hepatic mechanism for clearing the blood of bilirubin that even in the face of excessive bilirubin production in hemolytic disorders the appearance of jaundice is thought to be due to the associated liver damage which leads to the impairment of bilirubin excretion. In the "regurgitation" type of jaundice the bile pigment, even after its removal from the blood by the liver cells, is "regurgitated" back into the blood stream either because of the hepatic disease (hepatogenous jaundice) or the blockage of the bile ducts.

The laboratory tests which can be used to good advantage in the differential diagnosis of jaundice have been shown by several investigators to fall into two rather distinct groups: (1) the tests measuring the various functions of the liver parenchyma, and (2) the tests estimating the degree of interference with the flow of bile from the liver into the bowel.

Tests in the first group include a great variety of laboratory procedures. Knisely<sup>2</sup> lists 500 individual determinations. The ones most commonly employed are the hippuric acid test, serum total proteins with albumin/globulin ratio, serum gamma globulins and flocculation tests, such as cephalin cholesterol and thymol turbidity. The bromsulphalein dye retention test,

although a sensitive indicator of liver cell damage, cannot serve to distinguish between hepatogenous jaundice and that due to extrahepatic obstruction because the dye is excreted by the liver into the bile; therefore, its removal from the blood depends not only upon the functional state of the parenchymal liver cells but also on the patency of the biliary system, and the circulatory efficiency in carrying the dye to the liver.

Before discussing the tests in the second group, it would be appropriate to review briefly the physiology of the bile pigment.

Hemoglobin released from the red blood cells is changed to bilirubin-globin (indirect-reacting bilirubin), presumably by the reticuloendothelial cells. Indirect-reacting bilirubin brought to the liver by the blood stream is taken up by either the polygonal liver cells or the Kupffer cells, but before being secreted into the bile capillaries undergoes a chemical change into another allied compound, perhaps sodium bilirubinate (direct-reacting bilirubin).<sup>\*</sup> Whereas indirect-reacting bilirubin is never excreted in the urine, direct-reacting bilirubin is, once its concentration in the blood surpasses the renal threshold. The latter is considered to be rather low for the direct-reacting pigment.<sup>\*</sup> As a result, in the regurgitation type of jaundice (infectious hepatitis), bilirubin will be recovered in the urine even before clinical jaundice sets in, whereas in the retention type of jaundice theoretically it will be absent from the urine no matter how high its concentration, provided there is no associated liver damage which would lead to the development of jaundice of dual etiology ("mixed" retention and regurgitation type).

The bacterial flora in the colon convert sodium bilirubinate into urobilinogen, in which form it is recovered in the stool. However, some of the urobilinogen formed in the bowel is reabsorbed into the blood stream and is thus carried back to the liver which promptly removes it from the blood for reexcretion into the bile, either as the same chemical individual or after its conversion back into bilirubin (enterohepatic circulation of urobilinogen). So effective is this mechanism that very little of the reabsorbed urobilinogen will escape removal by the normally functioning liver, and thus only minute amounts will spill into the urine. In the retention type of jaundice, which results from excessive hemolysis with increased production of bilirubin-globin, more pigment will reach the bowel, and therefore more urobilinogen will be produced by the bacterial flora of the colon. Thus increased amounts of urobilinogen will be recovered from the stool, and also from the urine, if this condition happens to be complicated by some degree of hepatic dysfunction, for the liver then may not be able to handle all the reabsorbed urobilinogen brought to it by the blood for reexcretion into the bile. On the other hand, in complete obstruction of the

<sup>\*</sup> In separating by chromatography direct and indirect-reacting bile pigment from serum and from bile, it was recently demonstrated that neither pigment contained protein and that the van den Bergh reaction apparently did not depend on the splitting by alcohol of a linkage with protein, but rather was due to the existence of two types of pigment (J. Clin. Path. 6: 99, 1953).

bile ducts no bilirubin will reach the bowel; however, minimal amounts of urobilinogen will still appear in the stool because of the bilirubin derived from the desquamated bile-stained epithelial cells of the alimentary canal. In these circumstances practically no urobilinogen will be found in the urine. With only partial obstruction, smaller than normal amounts of pigment will be recovered in the stool; at the same time, greater than normal amounts of urobilinogen may spill into the urine if there is an associated liver damage.

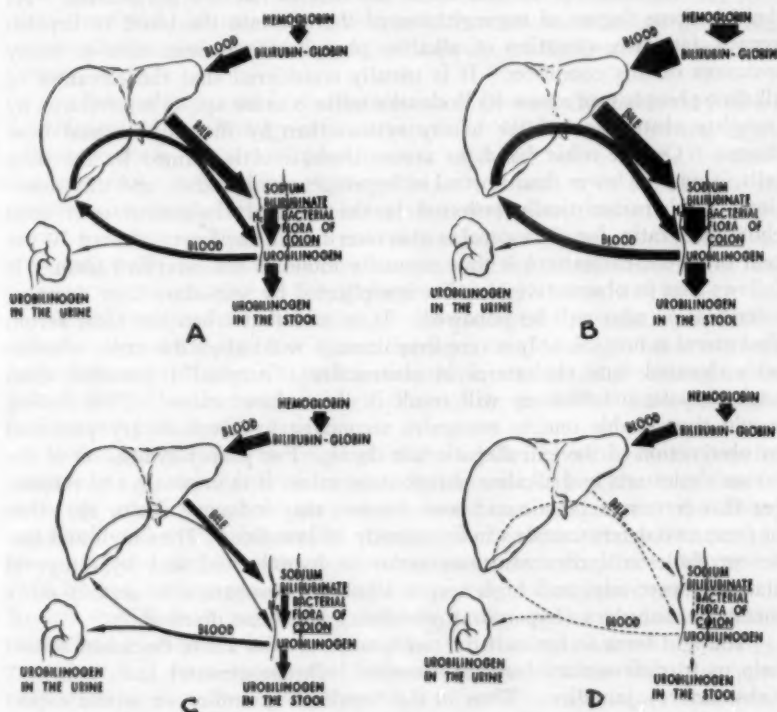


FIG. 1. Bile pigment metabolism. (A) Normal. (B) Hemolytic jaundice. (C) Hepatogenous jaundice (incomplete obstruction). (D) Obstructive jaundice (complete intrahepatic or extrahepatic obstruction).

In hepatogenous jaundice there is always present at least some degree of interference with the flow of bile into the bowel. Moreover, here the increase in urinary urobilinogen will be particularly marked. With partial and intermittent obstruction produced by biliary calculus, characteristically varying amounts of urobilinogen will be found in the urine due to ball-valve effect of the stone. These relationships are schematically represented in figure 1.

Thus we can readily see that the determination of urobilinogen in the stool and urine can serve as one of the tests in the second group of laboratory procedures mentioned above, namely, procedures designed to detect interference with the flow of bile. The determinations of serum cholesterol and alkaline phosphatase serve the same purpose. Both are excreted in the bile, and therefore in obstructive jaundice the values for both will be elevated. This elevation is thought by some to be due partly to the excessive formation of these substances by the liver under the stimulation of regurgitation. As there is some degree of regurgitation of the bile into the blood in hepatogenous jaundice, elevation of alkaline phosphatase is seen also in many instances of this condition. It is usually considered that the elevation of alkaline phosphatase above 10 Bodansky units is more apt to be produced by complete obstruction of the biliary system than by the parenchymal liver disease. On the other hand, as serum cholesterol is formed by the liver cells, it may be lower than normal in hepatogenous jaundice, and this sometimes is characteristically reflected in the lowered cholesterol ester/total cholesterol ratio, for cholesterol is also esterified in the liver. About 70 per cent of serum cholesterol is thus normally found in the esterified form. It follows that in obstructive jaundice complicated by secondary liver damage, esterification also will be impaired. It is said that when the total serum cholesterol is normal, only severe liver damage will reduce the ratio, whereas with elevated total cholesterol in obstructive ("surgical") jaundice, even slight hepatic insufficiency will result in the reduced ratio.<sup>3</sup> This finding would thus enable one to recognize secondary liver cell injury produced by obstruction of the extrahepatic bile ducts. For proper evaluation of the serum cholesterol and alkaline phosphatase values it is imperative to remember that certain metabolic and bone diseases may influence one or the other of these two determinations independently of jaundice. Thus high and low serum cholesterol concentrations occur in hypothyroid and hyperthyroid states, respectively, and high serum alkaline phosphatase in certain other metabolic disorders (hyperparathyroidism) and bone diseases.

It might seem so far as if the two groups of tests above discussed should help us to differentiate between "medical" (hepatogenous) and "surgical" (obstructive) jaundice. Thus in the "medical" jaundice we would expect some of the tests of the first group (hippuric acid, serum proteins, cephalin cholesterol flocculation, thymol turbidity, ester cholesterol/total cholesterol ratio) to give abnormal results, and the tests of the second group (alkaline phosphatase, and fecal urobilinogen) to give normal results or results which deviate only slightly from the normal. The converse of this relationship would then seemingly hold in the case of "surgical" jaundice. There the matter might rest if it were not for the two complicating factors already alluded to.

In the first place, regurgitation jaundice originally of extrahepatic origin, as in obstruction of the major bile ducts by tumor, stone or stricture, before too long secondary hepatic damage occurs, frequently may be sus-



pected even on physical examination alone when enlarged liver is palpated ("hydrohepatosis"). In these circumstances some determinations belonging to both groups of tests may well be expected to give positive results. Second, in hepatogenous jaundice some obstruction to the bile flow occurs in almost all cases and at times may even become as complete as in carcinoma of the major bile ducts. Thus complete obstruction of from two to 30 days' duration is encountered in about 10 per cent of patients with hepatitis.<sup>4</sup> In such patients, in addition to the laboratory evidence of disturbed liver function, there will also be present evidence of interference with bile flow (high serum alkaline phosphatase and only traces of urobilinogen in the stool and urine).

At this point it would be of interest to review briefly the history of our knowledge of the pathology of acute hepatitis. While to begin with, hyperbilirubinemia in "catarrhal" jaundice was explained on an obstructive basis, the view had changed through the years only to return in our time to the original concept of obstruction (in certain cases), except that the obstructive factor has come to be regarded as representing a different mechanism from that originally postulated. Whereas the earlier clinicians, Stokes and Graves,<sup>5</sup> were referring to the gastroduodenal catarrh with jaundice, and Virchow<sup>6</sup> presented an elaboration of this concept by postulating a mucous inflammation of the papilla of Vater, Eppinger,<sup>7</sup> and later also other workers, have demonstrated that the pathologic process was actually residing in the liver. Recent studies with needle biopsy of the liver<sup>8,9,2a</sup> have confirmed and extended these observations.

Rich<sup>1</sup> thought that the regurgitation of bile in hepatogenous jaundice occurred as a result of the disruption of the continuity of the liver "cords" with the establishment of abnormal communications between the biliary canaliculi and the perisinusoidal spaces. Such abnormal communications have not been demonstrated in histologic sections. Kupffer cell-liver cell "block" has been proposed as another process to explain regurgitation.<sup>1</sup> Recent studies have suggested mechanisms of jaundice production which might lead to complete biliary obstruction in acute hepatitis. Thus Hanger and Gutman<sup>10</sup> have shown that in some forms of toxic hepatitis (post-arsphenamine jaundice) the polygonal liver cells remain intact both functionally and anatomically, but the biliary canaliculi within the liver lobule become blocked by inspissated bile. The original injury is presumably sustained by the bile capillary walls. This creates a picture simulating, in some of its effects, complete biliary obstruction of surgical jaundice, with normal liver function tests and abnormal results of tests indicating interference with the bile flow (high serum alkaline phosphatase, high serum cholesterol and the absence of fecal and urinary urobilinogen). Watson and Hoffbauer<sup>11</sup> found a somewhat similar picture in certain patients with viral hepatitis. However, they did not think that the bile plugs in the biliary canaliculi were numerous enough to explain regurgitation. In the face of the normal histology of polygonal liver cells and the normal liver

function tests, these authors considered the possibility of injury to the cholangioles, particularly their ampullary portions at the periphery of the lobule. This injury might allow the leakage or diapedesis of bile because of the increased permeability of the damaged cholangioles. Thus the obstruction would be of a functional rather than a mechanical nature. The authors considered this process analogous to the leakage of the glomerular filtrate back through the damaged tubules in the kidney, with resultant oliguria and azotemia. Still another explanation for the appearance of jaundice in viral hepatitis was offered by Steigmann and Popper,<sup>4</sup> who believed that in some cases regurgitation perhaps could be due to the compression by the inflammatory cells in the portal triads of the canals of Herring, the delicate links connecting the intralobular biliary canaliculi with the primary bile ducts within the portal space.

In fact, the notion that there may be an element of intrahepatic obstruction in hepatogenous jaundice goes back to the work of Rössle and also Klemperer. Rössle<sup>12</sup> reported instances of so-called cholangiolitic or cholangiotoxic cirrhosis with primary injury of the finest biliary passages within the lobules and plugs of inspissated bile in the intralobular passages, with consequent injury to the parenchymal cells. Biliary obstruction was thus primarily intralobular. Klemperer<sup>13</sup> reported cases of an undoubtedly intrahepatic obstruction in intrahepatic cholangitic biliary cirrhosis. In this form of chronic hepatitis there is primary involvement of the bile ducts (cholangitis) in the portal spaces, along with plugs of bile pigment in the intralobular capillaries. In contrast to the cholangiolitic form, the changes are thus more marked in the portal spaces than in the lobules. In addition, the hepatic cells may show degeneration or focal necrosis.

Whatever the mechanism of intrahepatic obstruction may be (and it may vary from case to case), the fact remains that there are instances of hepatogenous jaundice with the laboratory tests indicating biliary obstruction rather than parenchymal liver cell injury.\* On the other hand, we will encounter cases with gross obstruction of the extrahepatic biliary passages and secondary liver damage manifested both by physical findings (hepatomegaly) and by laboratory observations demonstrating hepatic dysfunction. How are we to distinguish "medical" from "surgical" jaundice in such circumstances?

First of all, it is important to realize that a well taken history still remains an essential witness in the court of clinical judgment, and that it is not to take a back seat to the laboratory procedures in any case. No current interpretations of hepatic tests are yet ready to be inscribed on the marble tables. In a jaundiced patient with laboratory evidence of biliary obstruction and normal liver function tests all pointing to a surgical condition, a

\* There are in this group also those patients in whom the complete obstruction lasts long enough to produce secondary metabolic manifestations, prolonged and marked elevation of serum cholesterol leading to the development of cutaneous xanthomas (xanthomatous biliary cirrhosis).

history of blood or plasma transfusions, of association with known cases of infectious hepatitis or of exposure to a hepatotoxin would strongly suggest primary liver disease, no matter what the laboratory tests indicate. But we cannot feel entirely secure in our assumption.

In addition, a closer scrutiny of the results of laboratory procedures may also prove helpful. According to some authors (Wason, Popper) cephalin cholesterol flocculation and thymol turbidity tests will most frequently remain negative, with certain exceptions, in liver damage secondary to extrahepatic obstruction, even in the presence of positive results of other hepatic function tests.<sup>1</sup> Although the liver cell damage appears to bear the most significant statistical correlation with abnormal thymol turbidity and cephalin cholesterol flocculation, as shown by Steigmann and Popper,<sup>4</sup> according to Popper<sup>14</sup> this correlation is absent in biliary hepatitis, even in the face of rather marked hepatic injury. One hundred eighty cases were studied by Hoffbauer, Rames and Meinert<sup>15</sup> with respect to what can be done with one sample of serum in the differential diagnosis of jaundice, employing such tests as the total and ester cholesterol, alkaline phosphatase, fractional bilirubin, cephalin flocculation and thymol turbidity; of all, the last two were found to be the most reliable. Thus in 77 cases of proved extrahepatic biliary obstruction there was but one that had both cephalin-cholesterol flocculation and thymol turbidity positive. However, this combination was more misleading in the other direction, inasmuch as these two tests were also negative in several cases of hepatogenous jaundice. This peculiarity of flocculation tests to give negative readings in instances of secondary liver damage, even when other tests indicating hepatic injury practically all became finally positive, is considered to be due probably to the depression of some flocculations by regurgitated biliary substances and also to the lack of a mesenchymal reaction.<sup>3</sup> It is believed that the latter process, frequently observed in acute hepatitis, is actually responsible for positive flocculation tests through the intermediary of an increase in gamma globulins presumably produced by these mesenchymal elements. When liver damage due to extrahepatic obstruction is further complicated by infection of portal triads which then become infiltrated by inflammatory cells, the cephalin cholesterol flocculation test may become positive.<sup>3</sup>

Although the laboratory tests above discussed are very helpful in arriving at the correct diagnosis and in determining the proper type of treatment in many cases, there remain a few in which the history, the physical examination and the most elaborate profile of hepatic tests all fail to provide the necessary clue. It is true that in such a case the time will often "make" the diagnosis; i.e., the natural course of the disease, as it unfolds itself over a sufficiently prolonged period, may furnish the missing links in the chain of evidence required for a successful resolution of the diagnostic problem. However, watchful expectancy is not always in the best interests of the patient. The introduction and development of the technic of aspiration liver biopsy and the increasing familiarity with the histologic features presenting

for examination by this method still further reduce, perhaps down to the irreducible minimum, the number of cases in which the correct diagnosis otherwise cannot be made, or at least cannot be made for some time. If the liver biopsy does not lead to a definitive diagnosis (and from the subsequent discussion it will be apparent that this happens time and again), then it may at least pave the way for the next step; thus it can indicate, for example, that the case in question is that of "surgical" jaundice, and the precise cause of biliary obstruction will be determined at operation.

The reports of liver biopsies in infectious hepatitis by a number of workers previously mentioned have established pathologic criteria for this disease. Briefly, the histologic findings consist of marked infiltration of the portal triads with monocytes, lymphocytes and eosinophils, and focal areas of polygonal cell necrosis which may be surrounded by similar inflammatory cells. Although in severe cases liver cell necrosis can be massive, the reticular framework remains intact. The histologic appearance in toxic (post-arsphenamine) hepatitis and cholangiolitic hepatitis, as described by Hanger and Gutman<sup>10</sup> and Watson and Hoffbauer,<sup>11,16</sup> respectively, has been already referred to earlier in this article. Recently the reports from Schiff's clinic have presented in detail the histologic picture of extrahepatic biliary obstruction.<sup>17,18</sup> The picture is that of inspissated bile plugs in intralobular biliary canaliculi, sometimes precipitated bile in the portal ducts, infiltration of portal triads with polymorphonuclear leukocytes and other inflammatory cells and, most characteristic of all, "bile lakes" consisting of small pools of extravasated bile encircled by an area of rather striking degenerative changes in the surrounding parenchymal liver cells. The report by these authors<sup>17</sup> of 181 needle biopsies of the liver obtained from 157 patients with jaundice probably represents the widest experience in this field. Further reference to it will be made in the subsequent discussion.

An attempt will now be made to present both the advantages and the limitations of needle liver biopsy in the differential diagnosis of jaundice by means of the illustrative cases.

#### CASE REPORTS

*Case 1.* A 44 year old cemetery worker entered the hospital on August 31, 1948, because of jaundice of six days' duration. Patient was well until a few weeks prior to entry, when he developed anorexia, increased fatigability and malaise, and lost weight. These symptoms followed a severe upper respiratory infection. He noticed dark colored urine 10 days before admission, and two days later jaundice and clay colored stools. Whereas previous to the onset of jaundice there was no history of food intolerance, after its appearance fried, greasy and fatty foods produced mild distress. He stated that as a cemetery worker he sometimes dug graves and on occasion got his feet wet as the water collected in the excavated areas. Past history was not remarkable except for jaundice in childhood. On admission the patient was seen to be markedly jaundiced. The temperature was 98.6° F. There was tenderness to palpation in the epigastrium and the right upper quadrant of the abdomen. Liver and spleen were not palpated. Small telangiectases were seen over the chest and

arms. Large purpuric areas were noted over the shoulders, back, arms and thighs. Urinalysis was not remarkable, except for bile. Complete blood count was within normal limits. Serum bilirubin was 11 mg. per cent; prothrombin time, 100 per cent of normal; serum total proteins, 6.5 gm. per cent, with 4.6 gm. per cent of albumin and 1.9 gm. per cent of globulin; cephalin cholesterol flocculation test, negative in 24 hours; and thymol turbidity, 4 units. Urinary urobilinogen was present in 1-10 dilution only. The blood smears for *Leptospira icterohaemorrhagiae* were negative (a rather unreliable test). Flat plate of the abdomen was not remarkable. While in the hospital the patient complained of mild pruritus. One week after admission the liver was palpable and slightly tender. Serum bilirubin rose to 20 mg. per cent, at which time the serum alkaline phosphatase was 5 Bodansky units. Cholecystograms failed to visualize the gall-bladder. The second determination of alkaline phosphatase was 6 Bodansky units two weeks after admission. Although jaundice did not appear to diminish, the patient began to feel better in the third week of hospitalization and his appetite improved.

*Comment:* The onset was rather "classic" for infectious hepatitis. The purpuric manifestations and occupational history were suggestive of Weil's disease. However, certain features of the latter were lacking, including negative urinary findings. The results of the laboratory tests were against the diagnosis of hepatitis. In our series we have encountered but three jaundiced patients with viral hepatitis and negative cephalin cholesterol flocculation. Moreover, the thymol turbidity was also within normal limits in this case. The liver biopsy was performed three weeks after admission. It showed that the liver cells did not look particularly remarkable except for slight swelling; there were no areas of necrosis; numerous bile canaliculi were seen plugged with inspissated bile (figure 2A). The picture was consistent with biliary obstruction and the patient was operated upon. He was found to have carcinoma of the common duct. Thus the subjective improvement while in the hospital (the patient felt generally better and regained his appetite) was deceptive, while the alkaline phosphatase determinations gave misleading results.

*Case 2.* A 39 year old white male had been treated for Hodgkin's disease in this hospital 18 months before the present admission. This time, soon after entry he first complained of some abdominal pain and nausea and then noticed dark urine, and a few days later he was seen to develop jaundice and low grade fever. The examination of the abdomen was not remarkable; there was no tenderness and the liver edge was not palpable. The serum bilirubin was 8.2 mg. per cent and within 10 days rose to 20 mg. per cent, at which time the total serum proteins were 6.3 gm. per cent, with 4.4 gm. per cent of albumin and 1.9 gm. per cent of globulin. Cephalin cholesterol flocculation was negative in 24 hours; thymol turbidity, 6 units; serum alkaline phosphatase, 8 Bodansky units; prothrombin time, 14 seconds (93 per cent of normal).

*Comment:* In this case the symptoms were compatible with infectious hepatitis. The absence of abdominal tenderness and palpable liver did not rule out this possibility, as some patients with viral hepatitis have no positive physical findings except jaundice (and others may not have jaundice). On the other hand, the results of laboratory tests (cephalin cholesterol flocculation and thymol turbidity) were not those usually seen in this disease.



Therefore, the question of extrahepatic obstruction was raised. The serum alkaline phosphatase was below 10 Bodansky units but the determination was made early in the course of the disease. The liver biopsy showed infiltration of the portal tracts with lymphocytes, plasma cells and polymorphonuclear leukocytes; there was some increase in the number of small bile ducts, also marked pigmentation of the liver cells in the central portions,

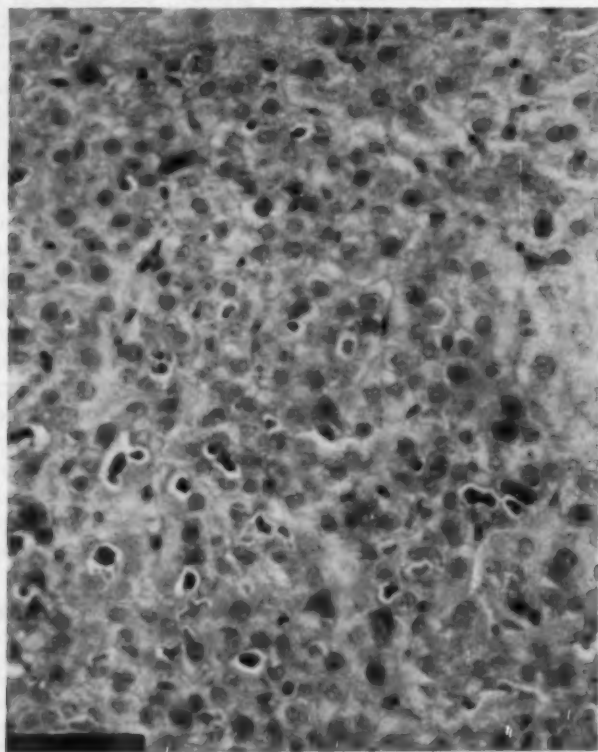


FIG. 2. Histopathology of the liver. (A) *Case 1*. Obstructive jaundice due to carcinoma of the common duct. There are numerous bile casts in biliary canaliculi. (Hematoxylin and eosin)  $\times 380$ .

along with numerous bile plugs in the canaliculi; otherwise, the liver cells were not remarkable. The picture was consistent with obstructive jaundice and subacute cholangitis. Since the patient had Hodgkin's disease, the obstruction of the major bile ducts by this process appeared to be a reasonable guess. The lymph nodes in the vicinity of the bile passages must be fixed and perhaps exhibit propensity for infiltrative spread, as in carcinoma, before



obstruction can occur; thus obstruction does not develop when the lymph node involvement is of an inflammatory nature. It is said that in leukemias it is not encountered for the same reason. But Hodgkin's disease is a different process. At any rate, the assumption above mentioned was acted upon by administering methyl bis (2 chloroethyl)-amine. Following this therapy the temperature dropped to normal in a few days, the patient felt better and the jaundice promptly cleared.

*Case 3.* A 34 year old Portuguese warehouseman was admitted into the hospital on February 7, 1952, because of jaundice. The patient dated the onset of the present illness from the time when, three weeks before entry, he noticed dark urine, light stools and jaundice accompanied by pruritus. At times there was some nausea but no vomiting. There was no history of chills, fever, abdominal pain or discomfort, hematemesis or melena. The appetite remained good. At the beginning of this illness he consulted a physician who prescribed a light diet, administered penicillin parenterally and ordered the cholecystograms which failed to visualize the gall-bladder. Finally hospitalization was advised because it was thought that the jaundice was increasing. Past history was not remarkable. The patient had never had jaundice before. The consumption of alcohol was limited to three highballs and two or three bottles of beer a week. On entry the patient was seen to be deeply jaundiced, mentally clear and well oriented. The temperature was 98.8° F. The abdomen was soft and not distended. A smooth nontender liver edge descended about three finger-breadths below the right costal margin with inspiration. The spleen was not palpated. There was no lymphadenopathy or edema. No telangiectasia, spider angiomas or palmar erythema were noted. The urinalysis was not remarkable. Complete blood count was within normal limits. Serum bilirubin was 45 mg. per cent; serum total proteins, 7.9 gm. per cent, with 5.6 gm. per cent of albumin and 2.3 gm. per cent of globulin; gamma globulins, 600 mg. per cent; thymol turbidity, 7 units; cephalin cholesterol flocculation, 1 plus in 24 hours; prothrombin time, 18 seconds (78 per cent of normal). No urobilinogen was found in the urine on a qualitative test. Urobilinogen in the stool collected over a 24 hour period measured 3 mg. Another determination of the serum bilirubin was made a week after admission and showed the value of 41 mg. per cent.

*Comment:* For the following reasons, the original impression was that the patient had extrahepatic biliary obstruction, probably malignant, rather than hepatogenous jaundice: (1) Not only were there practically no prodromal symptoms of infectious hepatitis, but the patient also retained good appetite. (2) A patient with viral hepatitis and the degree of hyperbilirubinemia this case exhibited usually feels and looks ill. (3) The laboratory tests (serum proteins, including gamma globulin, thymol turbidity and cephalin cholesterol flocculation) were indicative of extrahepatic rather than intrahepatic etiology. Marked jaundice of acute hepatitis is usually accompanied by the laboratory evidence of parenchymal liver damage, with the exception of the comparatively rare cases of cholangiolitic hepatitis. (4) On the other hand, the quantitative fecal urobilinogen studies demonstrated complete biliary obstruction. Surprisingly enough, liver biopsy performed on the eighth hospital day showed the changes of marked and diffuse hepatitis (figure 2B). Although the course of the disease was prolonged, it

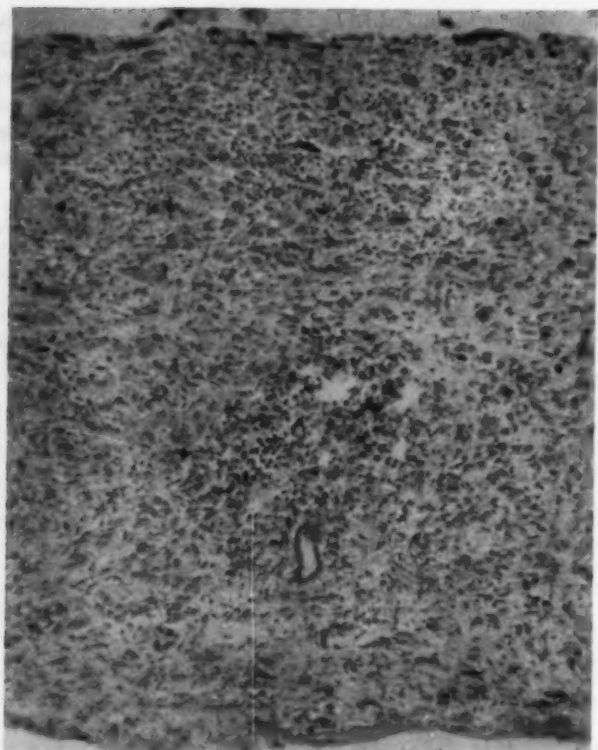


FIG. 2B. *Case 3.* Infectious hepatitis. Note disorganization of the lobular pattern, necrosis of polygonal liver cells and marked intralobular infiltration with inflammatory cells; similar infiltrative process is also seen in the portal space. (Hematoxylin and eosin)  $\times 120$ .

nevertheless was uneventful, characterized by gradual although slow improvement. At the time of discharge the serum bilirubin was 0.5 mg. per cent.

*Case 4.* A 52 year old white male entered the hospital on October 24, 1951, because of chills, fever, jaundice and mild pruritus of five days' duration. There was no history of jaundice in the past. For 10 years the patient has had periodic attacks of epigastric pain, not associated with any vomiting, chills, fever, diarrhea or jaundice, and apparently not related to food. The last such episode had occurred two years before admission, and for this period of two years he has remained entirely free from symptoms. On entry the patient was seen to be a slender male, jaundiced, but in no apparent discomfort. The temperature was 98° F. There was tenderness on palpation in the epigastrium and the right upper quadrant of the abdomen. Liver and spleen were not palpated. A few telangiectases were seen over the chest. Urinalysis was not remarkable except for bile; the red cell count was 4.3 million;

hemoglobin, 12 gm. per cent; white cell count, 8,450, with 72 per cent neutrophils and 28 per cent lymphocytes. Serum bilirubin was 14 mg. per cent; prothrombin time, 87 per cent of normal; serum total proteins, 6.7 gm. per cent, with 4 gm. per cent of albumin and 2.7 gm. per cent of globulin; cephalin cholesterol flocculation test was 1 plus in 24 hours; serum alkaline phosphatase, 4 Bodansky units. Urinary urobilinogen was present in 1-10 dilution. The cholecystograms failed to visualize the gall-bladder. The gastrointestinal series on the erect study revealed the presence of a small pocket containing air and fluid, adjacent to the duodenal bulb; this was interpreted as possibly indicating a pinpoint perforation of an ulcer crater. While in the hospital the patient remained afebrile except for the elevation of temperature to 102° and 100° F. on the fourth and fifth hospital days, respectively. The patient's only complaint was that of drowsiness.

*Comment:* The most recent history was strongly suggestive of a common duct stone, but there were several complicating features. In view of the roentgenologic findings the past history of epigastric pain could be interpreted in terms of a peptic ulcer, culminating in perforation and biliary obstruction. However, peptic ulcer is one of the rarest causes of jaundice. Failure of the gall-bladder to visualize is not too uncommon in the presence of regurgitation jaundice from whatever cause. For this reason the failure of the gall-bladder to visualize should not necessarily be construed as another evidence of cholelithiasis. At any rate, more important than the clinical determination of the precise nature of the obstructing lesion was the decision as to whether this case actually was that of "surgical" jaundice. Laboratory findings (cephalin cholesterol flocculation and serum alkaline phosphatase) were more in keeping with the intrahepatic disease than with extrahepatic obstruction. Liver biopsy revealed the presence of a large amount of brown-staining pigment in the central lobular areas; the parenchymal liver cells otherwise were not remarkable, but bile canaliculi contained casts of pigment. At operation a common duct stone, measuring 1 cm. in diameter, was found, in addition to several calculi in the gall-bladder. In passing, it is of interest to note here that the histologic picture of the liver was similar to that in the patients with malignant obstruction of the bile ducts (cases 1 and 2). The implication of these comparative findings will be discussed later.

*Case 5.* A 43 year old white male entered the hospital on May 24, 1951, because of jaundice. Four days before admission the patient noticed jaundice, dark colored urine and clay colored stools. His appetite declined rapidly and he developed some nausea. There was no history of any abdominal pain, chills, fever or any antecedent respiratory infection. Two months prior to the onset of this illness he had served as a blood donor. He had never had jaundice or any gastrointestinal symptoms in the past. Alcoholic history was not obtained. On entry the patient was seen to be moderately icteric. The temperature was 98.2° F. No telangiectasia or spider angiomas were seen. The liver was easily palpable and tender. The spleen was not palpated. The urinalysis was not remarkable. The red cell count was 4.0 million; hemoglobin, 12 gm. per cent; white cell count, 13,300, with 75 per cent neutrophils and 25 per cent lymphocytes. Serum bilirubin was 10 mg. per cent; total serum proteins, 6 gm. per cent, with 4 gm. per cent of albumin and 2 gm. per cent of globulin; cephalin cholesterol flocculation test, negative in 24 hours; thymol turbidity,

8 units; serum alkaline phosphatase, 3 Bodansky units; prothrombin time, 60 per cent of normal.

*Comment:* This was an acute episode with an abrupt onset and the symptomatology suggestive of infectious or homologous serum jaundice in a man who had never had any gastrointestinal symptoms of any sort in the past and who did not have the physical stigmata of Laennec's cirrhosis. It

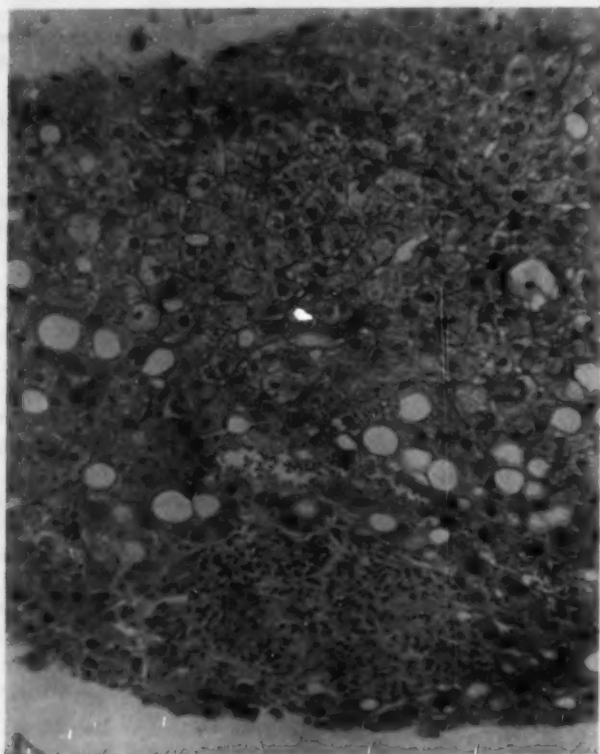


FIG. 2C. Case 6. Focal hepatitis. A localized area of liver cell necrosis and infiltration with inflammatory cells is well shown. In addition, there are moderate fatty changes; these reflect the nutritional state of the patient. (Hematoxylin and eosin)  $\times 120$ .

is true that cirrhosis often becomes clinically manifest abruptly in a person previously in good health, but in such instances infectious hepatitis is frequently and quite legitimately also suspected, particularly in the absence of the "cirrhotic" appearance. Also, the plasma proteins were practically normal. On the other hand, however, cephalin cholesterol flocculation was negative in 24 hours, and thymol turbidity value was only slightly elevated. This combination certainly occurs much more frequently in cirrhosis than

in acute hepatitis. The liver biopsy settled the question by demonstrating portal cirrhosis. From the therapeutic point of view this was of no practical significance at the moment, but from the standpoint of prognosis and long-term management the diagnosis discovered by means of biopsy was worth having.

*Case 6.* A 59 year old white male entered the hospital on May 4, 1953, because of generalized dermatitis of three days' duration. A few weeks before admission he had been given Sulfasuxidine for a febrile illness. Following this therapy a generalized rash appeared. On entry the patient was seen to be an acutely ill, white elderly male. The temperature was 101° F. The sclerae were icteric. The liver was enlarged and slightly tender. The trunk and extremities were covered with a macular papular erythematous rash in different stages of development. Urinalysis showed a trace of protein, some white blood cells, red blood cells and a few hyaline and granular casts. The red cell count was 4.17 million; hemoglobin, 13 gm. per cent; white cell count, 7,700, with normal differential. The blood urea nitrogen was 43 mg. per cent; serum bilirubin, 4 mg. per cent; prothrombin time, 93 per cent of normal; serum total proteins, 6.1 gm. per cent, with 3.7 gm. per cent of albumin and 2.4 gm. per cent of globulin; cephalin cholesterol flocculation test, 4 plus in 24 hours; thymol turbidity, 20 units.

*Comment:* Dr. E. Jung, who was in charge of this patient, has had some experience with the untoward reactions to Sulfasuxidine, and recognized the rash as probably being due to the drug. It was thought that the hepatic involvement might be on the same basis. The aspiration liver biopsy showed the presence of a moderate amount of fat and focal areas of necrosis of liver cells associated with moderately dense infiltration by lymphocytes, polymorphonuclear leukocytes, a few plasma cells and an occasional eosinophilic leukocyte; the lobular pattern otherwise was normal (figure 2C). The patient was treated with cortisone. The temperature dropped to normal on the second hospital day, the rash faded, the jaundice cleared, and the blood urea nitrogen at the time of discharge was 10 mg. per cent. Hartley and Lusburgh<sup>19</sup> have demonstrated focal lesions in experimental allergic necrosis of the liver.

*Case 7.* A 56 year old male was admitted into the hospital on October 27, 1952, because of jaundice and pruritus. The patient dated the onset of his illness from September 15, when he developed a generalized pruritus. Approximately two weeks later jaundice appeared. At the same time the pruritus became much more distressing. He also noticed clay-colored stools. There was no history of pain, chills or fever. There was a loss of 15 pounds of weight. The past history was not remarkable except for myocardial infarction in 1946. On physical examination the patient was seen to be a slender male not appearing to be in any acute distress. The temperature was 98.2° F. Mild jaundice was apparent. A slightly tender liver edge was palpated two fingerbreadths below the costal margin. The spleen was not palpated. Urinalysis was not remarkable. Hemoglobin was 15.5 gm. per cent and the white cell count 9,100. Serum bilirubin was 5 mg. per cent; serum total proteins, 6.5 gm. per cent, with 4.5 gm. per cent of albumin and 2.0 gm. per cent of globulin; thymol turbidity, 3 units; cephalin cholesterol flocculation test, negative in 24 hours; serum cholesterol, 250 mg. per cent; prothrombin time, 87 per cent of normal. Bromsulphalein test (5 mg./kg. dose) showed 20 per cent retention of the dye in 45 minutes. Serum alkaline phosphatase was 21 Bodansky units.



*Comment:* At operation a carcinoma of the head of the pancreas was found; common duct was distended. The aspiration liver biopsy performed before surgery failed to disclose any remarkable findings: the histologic picture was within normal limits. This case illustrates that normal liver histology may be encountered in patients with extrahepatic biliary obstruction comparatively early in the course of the disease, when the obstruction is not complete. The decision to operate was made because the hepatic tests, with the exception of bromsulphalein dye excretion, were normal, as was the histologic picture of the liver, in the presence of jaundice and in the absence of a hemolytic disorder or such other "icterogenic" extrahepatic conditions as pulmonary infarction. Besides, icterus was accompanied by pruritus; this combination happens in regurgitation jaundice. It is interesting to note that pruritus set in before the appearance of icterus. Of course, the patient might well not have noticed it when it actually first appeared, but on the other hand, in obstructive jaundice pruritus is well known sometimes to precede jaundice by a varying interval. Such an occurrence is referred to as dissociated jaundice,<sup>20</sup> and implies a selective retention of either bilirubin or bile salts. It is also of interest to observe the results of the bromsulphalein test in this patient (20 per cent retention of the dye in 45 minutes). It was pointed out earlier that this determination was not of any particular value in the presence of rather marked bilirubinemia. However, marked retention of the dye in incomplete biliary obstruction with only slight jaundice points to secondary hepatic damage. This was the only determination in the group of tests employed in our patients which indicated hepatic dysfunction. Thus we are once more reminded about the great sensitivity of this test for the recognition of liver cell damage. On the other hand, normal clearance of the dye in the presence of jaundice indicates a common duct stone.<sup>8</sup>

The patient reported below exemplifies the type of case in which liver biopsy probably should not be done for fear of spreading infection.

*Case 8.* A 75 year old white male entered the hospital on August 2, 1951, because of fever and jaundice. He became ill 12 days before entry, when he lost his appetite, felt nauseated and vomited. A few days later he developed fever and noted dark urine, clay-colored stools and scleral icterus. There was no pruritus. There was no history of jaundice in the past. He admitted having been a heavy drinker for many years. His private physician sent him into the hospital with the diagnoses of infectious hepatitis and pneumonia. On admission the patient was seen to be an acutely ill, obese elderly male. The temperature was 102° F. The lungs were clear except for a few atelectatic râles in the right base. The heart was not remarkable. The abdominal examination showed some distention and slight tenderness in both upper quadrants; the liver was not palpated, but the palpation was difficult because of obesity. Sacral edema was present. Spider angiomas were seen over the upper chest. Urinalysis showed a slight trace of albumin and many granular, hyaline and epithelial casts. The red cell count was 4.3 million; hemoglobin, 12.7 gm. per cent; white cell count, 25,300, with 92 per cent neutrophils. The sedimentation rate was 108 mm. in one hour (Westergren). Blood urea nitrogen, 55 mg. per cent; serum bilirubin, 5 mg. per cent; prothrombin time, 17 seconds (83 per cent of normal);



serum total proteins, 6.4 gm. per cent, with 2.8 gm. per cent of albumin and 3.6 gm. per cent of globulin; cephalin cholesterol flocculation test, plus-minus in 24 hours (1 plus in 48 hours); thymol turbidity, 6 units; serum alkaline phosphatase, 4 Bodansky units; total serum cholesterol, 75 mg. per cent, with 55 mg. per cent of cholesterol esters; the test for urinary urobilinogen was positive in 1-1280 dilution. The roentgenogram of the chest was within normal limits. Flat plate of the abdomen showed no evidence of ileus, and was not in any way remarkable. Following a course of penicillin therapy and administration of fluids parenterally patient became afebrile at the end of the second week in the hospital. However, three days later he became worse, lethargic and then comatose. He died on August 26. The autopsy disclosed the presence of several common duct stones, calculous gall-bladder, cholangitis and multiple liver abscesses, some measuring up to 1 cm. in diameter.

*Comment:* This patient illustrates the fact that in extrahepatic obstruction complicated by cholangitis and infection of the liver, a clinical picture of severe sepsis may result, distracting one's attention from the underlying obstructive factor. Thus the evidence of "surgical" type of obstructive jaundice is transformed into that of "medical" type of jaundice, as has been well pointed out by Popper.<sup>21</sup> When the realization of what was actually going on in this case finally dawned upon the staff, the patient's general condition was too critical to allow surgical intervention.

The illustrative cases herein presented serve to demonstrate both the advantages and the limitations of needle liver biopsy as a diagnostic procedure.

It is obvious that there are patients with jaundice in whom a definitive diagnosis cannot be made by any other means. This statement can be further amplified by reference to those instances where the clinician arrives at a seemingly reasonable diagnosis based upon what would appear to be a proper evaluation of the historical, physical and laboratory data, only to be humbled by a liver biopsy which exhibits the histologic features all but contrary to his hunches and deductions. No degree of funded knowledge and diagnostic acumen makes one exempt from such onslaughts. Liver biopsy, however, not only deflates spurious confidence but also bolsters the courage of an otherwise wavering determination when the pathologic picture in the biopsied specimen happens to fall in line with the conclusions reached on other grounds.

Once more the pathologist has the last word, but this time it serves the interests of a living patient instead of merely pronouncing the last judgment at a meeting of the minds in a clinicopathologic exercise. It is regrettable that a similar approach is not available in all the other fields of diagnostic endeavor, and that in the one under discussion the pathologist is not always right either, for he also has his difficulties.

This is documented by the work of Weisbrod, Schiff, Gall, Cleveland and Berman,<sup>17</sup> who found that errors in differentiating infectious hepatitis from obstructive jaundice on pathologic study of biopsied material occurred and that they were more apt to occur late in the course of viral hepatitis or in

the milder cases of the disease. These errors were "readily explainable by the disappearance or marked diminution of the intralobular changes and the persistence of the periportal changes during the later phase of the disease, which may be mistaken for obstructive jaundice." The most striking histologic findings in such cases may consist of only periportal infiltration, simulating the pericholangitis seen in obstructive jaundice. Dible, McMichael and Sherlock<sup>9</sup> have also observed this histologic appearance in the mild cases and the convalescent phases of viral hepatitis. On the other hand, Weisbrod et al.<sup>17</sup> encountered morphologic changes early in the course of obstructive jaundice which might be wrongly ascribed to infectious hepatitis. "Bile lakes," as described by Roholm and Krarup<sup>22</sup> and Weisbrod et al.,<sup>17</sup> which are so characteristic of the extrahepatic biliary obstruction, unfortunately are found in the later stages of the disease. Therefore, this finding is perhaps not so serviceable, for it seems to us that at this point in the course of illness the diagnosis most likely can be made without the biopsy.

The liver biopsy does not distinguish between calculous and neoplastic obstruction, as can be seen in the illustrative cases 1, 2 and 4, the first two with obstruction of the bile ducts by tumor and the third by a stone. In all three the essential histologic changes are similar. This does not present a serious problem, since the important practical issue is that of differentiating between the "medical" and "surgical" types of jaundice, rather than establishing preoperatively the precise nature of obstruction.

Needle liver biopsy is not entirely an unmixed blessing, for it is not an altogether innocuous procedure. It carries with it certain morbidity, fortunately very small. Deaths are known to have occurred as a result of it. Is the game worth the candle? Is such a risk warranted? Think what might have happened to case 3 if he had been operated on because of the mistaken diagnosis of extrahepatic obstruction. Patients with hepatitis and particularly that degree of hyperbilirubinemia do not stand surgery well and may die as a result of it. Experience provides an affirmative answer to our question, but only if the liver biopsy is carried out when really indicated.

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## EXTRAHEPATIC BILIARY OBSTRUCTION: EXPERIENCE WITH NEEDLE BIOPSY OF THE LIVER\*

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THE introduction of needle liver biopsy by Roholm and Iversen<sup>1</sup> in 1939 has broadened considerably the diagnostic horizon in diseases of the liver and biliary tract, as well as in other conditions not primarily hepatobiliary in nature. The extent to which this procedure has been adopted in the United States is attested by, among other things, a recent report on the activities of the Liver Registry of the Armed Forces Institute of Pathology.<sup>2</sup> Over 2,000 biopsy specimens have so far been analyzed at the Institute, although to date many more are already available. The greatest individual group in this series concerns viral hepatitis.

Of particular interest is the application of needle liver biopsy to the problem of differential diagnosis of jaundice. Detailed description of the histopathology of the liver based on the study of material obtained by such means has been given by a number of investigators. Roholm and Iversen,<sup>1</sup> Mallory,<sup>3</sup> Dible, McMichael and Sherlock,<sup>4</sup> Weisbrod, Schiff, Gall, Cleveland and Berman<sup>5</sup> and Popper and Schaffner<sup>6</sup> have established the morphologic criteria for infectious hepatitis. Roholm and Krarup,<sup>7</sup> Popper and Franklin<sup>8</sup> and Weisbrod, Schiff, Gall, Cleveland and Berman<sup>5</sup> have described in detail the liver histology in obstructive jaundice.

In viral hepatitis the basic features consist of focal necrosis of the liver cells and infiltration of the portal triads with round cells. The former process may assume a massive character (acute or subacute atrophy). In many instances of severe hepatitis (which, however, have not progressed to the stage of acute atrophy), there may be such a marked infiltration of liver lobule by inflammatory cells, along with considerable disarrangement of the orderly pattern of liver plates, that at first glance one would hardly recognize the tissue as liver. Characteristically, the supporting reticulum remains intact. Occasionally bile plugs are seen in intralobular biliary canaliculi, simulating the appearance of extrahepatic biliary obstruction, but this feature usually is much less prominent than in obstructive jaundice. Moreover, bile precipitation in bile ductules of the portal spaces, observed in some cases of extrahepatic obstruction, is not seen in viral hepatitis. However, a form of hepatitis had been described by Watson and Hoffbauer<sup>9</sup> characterized by a remarkable absence of polygonal cell damage and the presence of bile plugs in the intralobular biliary canaliculi, thus simulating the ap-

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pearance of extrahepatic obstructive jaundice. This so-called cholangiolitic type of hepatitis is probably rare.

In extrahepatic biliary obstruction, the picture is also rather characteristic. The most striking feature is the plugging of intralobular biliary canaliculi by inspissated bile. Portal ducts are dilated and may also contain precipitated bile or even microcalculi.<sup>6</sup> In cases of longer duration extravasations of bile occur, surrounded by a zone of reactive fibrosis or degenerated liver cells. These areas, given the name of "bile lakes" by Roholm and Krarup,<sup>7</sup> have been noted by Weisbrod, Schiff, Gall, Cleveland and Berman<sup>8</sup> to occur very characteristically only in extrahepatic obstruction, thus constituting an important diagnostic sign. In addition, the portal triads are often swollen and infiltrated with inflammatory cells. In contrast to viral hepatitis, polymorphonuclear neutrophils may be well represented in such an infiltrate. In the vicinity of portal triads and elsewhere, liver cells may undergo degenerative changes. Heavy staining of polygonal cells by bile granules is frequently observed, particularly in the central zone. In contrast to viral hepatitis, steatosis of varying degree may be present.

In most cases, differentiation between hepatocellular and extrahepatic obstructive jaundice can be made on the examination of needle liver biopsy without much difficulty. However, some degree of overlap in histologic features occurs, as already intimated, rendering differential diagnosis on purely morphologic grounds rather difficult in some instances. Bile stasis may prove to be a prominent finding in some cases of viral hepatitis and be mistaken for evidence of obstructive jaundice. This error can be avoided by observing that the alterations in polygonal cells usually far outstrip the obstructive phenomena.<sup>6</sup> It has been pointed out that difficulties will be encountered in mild cases and in the convalescent phases of infectious hepatitis, where the most striking histologic features may be presented not by any changes within the liver cells but rather by periportal infiltration simulating pericholangitis of extrahepatic biliary obstruction.<sup>4,6</sup> On the other hand, focal areas of polygonal cell degeneration occurring in obstructive jaundice may be mistaken for viral hepatitis.

It is the purpose of this paper to describe our experience with needle biopsy of the liver in extrahepatic biliary obstruction and, among other things, to point out rather early development of beginning biliary "cirrhosis" in some cases. Roholm and Krarup<sup>7</sup> reported on a series of 27 patients with proved obstructive jaundice, and Weisbrod, Schiff, Gall, Cleveland and Berman<sup>8</sup> have more recently reported on a group of 17 proved and 13 probable cases of obstructive jaundice.

Our series consisted of 28 patients. All patients but one (case 5) were males. The ages varied from 32 to 75. In seven patients the obstruction was benign (calculous in six and due to a stricture of the common duct in one). In 21 patients obstruction was caused by neoplasm (carcinoma of the head of the pancreas, the ampulla of Vater, common and hepatic ducts, metastatic carcinoma obstructing major bile ducts and Hodgkin's disease).



In 27 patients the precise nature of the obstructive lesion was demonstrated either at the time of operation or at autopsy. In the remaining patient (case 9) the diagnosis was made on clinical grounds only.\* The duration of jaundice prior to liver biopsy and the results of hepatic tests are recorded in table 1. Bromsulphalein dye excretion test and the quantitative determinations of urinary and fecal urobilinogen were performed in too few patients to be recorded in the table. One patient (case 11) had two needle biopsies before the operation and a surgical biopsy. All biopsies (with the one exception above noted) were performed with the Vim-Silverman needle before surgery.

In 26 patients out of a total 28, the histologic changes in the biopsy specimens were interpreted as representing obstructive jaundice. The histopathology was very much like that already described. In one case the opinion on the biopsy specimen was indecisive. In the other patient (case 17) the biopsy was considered to be practically within normal limits. But even this interpretation was of a definitely positive value, because the normal biopsy in the presence of jaundice and hepatic tests indicating interference with bile flow (alkaline phosphatase, 21 Bodansky units), and in the absence of any of the other "icterogenic" conditions such as a hemolytic process, pulmonary infarction, etc., strongly pointed to obstructive jaundice. Rather marked bromsulphalein dye retention (20 per cent retention in 45 minutes on a 5 mg./kg. dose) argued in favor of secondary hepatic damage, not as yet manifest morphologically. Although in the presence of jaundice the bromsulphalein dye excretion test is of little value, generally speaking, Popper and Schaffner<sup>10</sup> point out that marked retention in incomplete biliary obstruction with only slight jaundice may indicate secondary hepatic damage. Parenthetically, it can be mentioned that, on the other hand, nearly normal clearance of the dye in the presence of jaundice is said to indicate a stone in the common duct.<sup>10</sup> That this may also occur in extrahepatic obstruction produced by malignancy is shown by case 11 where with the serum bilirubin of 6 mg. per cent bromsulphalein excretion was within normal limits (4 per cent retention).

With all due regard to the important place of history and physical examination in the investigation of the causes of jaundice, one of the purposes of this communication is not so much to evaluate the whole picture presented by the group of conditions under discussion as to consider the relative merits of hepatic tests and needle liver biopsy. In this connection, quick reference to table 1 will make certain relations quite clear. The question of serum bilirubin determinations can be dismissed by stating that, although particu-

\* We feel that jaundice in this case was due to obstruction of the extrahepatic bile ducts by lymph nodes involved by Hodgkin's disease. Diagnosis of Hodgkin's disease was made on previous admission, 18 months before the onset of jaundice. Jaundice and pruritus appeared during the second hospitalization. The results of hepatic tests were not those usually seen in viral hepatitis. Liver biopsy was interpreted as indicating biliary obstruction. Following the administration of nitrogen mustard 10 days after the onset of jaundice, icterus cleared rapidly within a matter of a few days.



TABLE I  
Obstructive Jaundice

Case	Age	Duration of Jaundice, Weeks Prior to Liver Biopsy	Serum Bilirubin, mg./100 c.c.	Plasma Prothrombin Time (% of Normal Control)	Serum Proteins, Gm./100 c.c.			Thymol Turbidity (Units)	Cephalin Cholesterol Flocculation		Serum Total Cholesterol, mg./100 c.c.	Serum Alkaline Phosphatase (Bodansky Units)	Cause of Obstruction Determined at Operation or Autopsy
					Total	Albumin	Globulin		24 hr.	48 hr.			
1	38	5	21	88	6.6	4.0	2.6	6	+	+	258	9	Neoplastic
2	39	1	15	76	7.9	4.9	3.0	11	+	+		8	Neoplastic
3	39	4	20	70	7.4	4.9	2.5	3	-	-	403	12	Neoplastic
4	44	3	18	80	6.5	4.7	1.8	4	-	-		8	Neoplastic
5	50	6	11	93				9	+	+		26	Neoplastic
6	60	2	8	94	7.0	4.4	2.6	3	+	+		36	Neoplastic
7	52	2	14	87	6.8	4.1	2.7	5	+	+	243	10	Common duct stone
8	54	2	16	86	6.6	4.5	2.1	6	+	+	167	8	Neoplastic
9	39	1	8	93	6.3	4.4	1.9	3	-	-		4	Common duct stone
10	32	1	7	100	6.9	4.5	2.4	4	-	-	215	8	Neoplastic
11	34	2	6	65	6.7	4.3	2.4	4	-	-	243	11	Neoplastic
12	56	1	10	100	4.6	3.2	1.4	4	-	-	506	31	Neoplastic
13	54	5	13	33					-	-			Neoplastic
14	59	16	22	71	5.8	3.8	2.0	6	-	-	360	8	Common duct stone
15	52	3	23	75	5.3	3.6	1.7		-	-	40	40	Neoplastic
16	65	2	10	90	5.0	3.0	2.0	4	-	-	180	36	Neoplastic
17	56	5	5	87	6.5	4.5	2.0	3	-	-	230	21	Neoplastic
18	35	1	10	81	6.8	5.0	1.8	4	-	+	174	11	Common duct stone
19	63	2	26	59	4.5	3.2	1.3	5	+	+	168	13	Neoplastic
20	55	2	1	100	6.0	4.4	1.6	3	-	+	144	2	Stricture of common duct
21	35	1	10	81	6.8	5.0	1.8	4.0	-	-	118	11.5	Common duct stone
22	75	4	5	100	7.3	4.6	2.7	4.0	-	-	147	4.2	Common duct stone
23	39	12	7	93	7.1	4.8	2.3	8.0	+	+	344	18.0	Neoplastic
24	63	2	18	59	4.5	3.2	1.3	5.0	+	+	240	13.0	Neoplastic
25	58	4	24	81	6.6	4.3	2.3	4.0	+	+	149	8.0	Neoplastic
26	60	2	9	76	7.0	4.7	2.3	6.0	-	-	199	12.0	Neoplastic
27	57	?	13	100	6.4	3.8	2.6	10.0	-	-	320	18.0	Neoplastic
28	54	4 (?)	15	87	7.5	4.5	3.0	4.0	-	-	301	25.0	Neoplastic

larly high serum bilirubin is diagnostic of malignant obstruction (or acute and subacute liver atrophy), in our series this diagnostic aid was unavailable, as most values were within lower range. The determination of serum prothrombin concentration was helpful in only one instance (case 13). In this patient the initial prothrombin time of 33 per cent of normal was seen to rise to 93 per cent within 48 hours of institution of vitamin K therapy. Plasma proteins were determined in 26 patients. In only six was hypoproteinemia present (values below 6 gm. per cent). Definite hyperglobulinemia (values above 3 gm. per cent) was not found in any of these cases. These results may be considered to be of some significance, inasmuch as with parenchymal liver disease, hypoproteinemia, hypoalbuminemia and hyperglobulinemia are frequently noted. Giansiracusa and Althausen<sup>11</sup> consider the albumin/globulin ratio valuable for the differential diagnosis of jaundice. However, normal serum protein values in hepatocellular disease (particularly infectious hepatitis) and abnormal ones in obstructive jaundice complicated by infection (cholangitic variety) occur too frequently<sup>8, 10, 12</sup> to make this an iron-clad rule.<sup>8, 10, 12</sup> Serum cholesterol determinations were made in 21 patients. High values (above 300 mg. per cent) indicative of obstructive jaundice were encountered in only six cases. The results of thymol turbidity and cephalin cholesterol flocculation tests were slightly more encouraging. Thus, thymol turbidity of 7 or more units and positive flocculation tests (3 or 4 plus in 48 hours) were seen only in four cases. These two tests are considered to be particularly useful in the differential diagnosis of jaundice, surpassed only by urinary and fecal urobilinogen determinations. It is generally conceded, however, that when obstruction is complicated by infection (cholangitic obstructive jaundice), thymol turbidity or cephalin flocculation may become positive, in spite of the fact that usually flocculations appear to be depressed by regurgitated biliary substances.<sup>13</sup> Hoffbauer, Rames and Meinert<sup>14</sup> state that in their experience with 77 cases of proved extrahepatic biliary obstruction there was but one that had both cephalin flocculation and thymol turbidity positive. We had two such patients (cases 5 and 23) in a considerably smaller series of 28 cases. It is also to be noted that there was no correlation between the positive results of these tests and clinical or pathologic evidence of an associated infection (cholangitic obstructive jaundice). Thus, in patients with either or both tests positive, the degree of infiltration of portal triads with inflammatory cells, including polymorphonuclear leukocytes, was not necessarily any more prominent than in those with negative tests. And in a few patients with "triaditis" the tests were negative. In fact, in one patient (case 13) with neoplastic obstruction and unmistakable evidence of pericholangitis, manifest clinically by high fever of the Charcot type and pathologically by marked enlargement of portal triads exhibiting well pronounced inflammatory process, both tests gave unequivocally negative results. The alkaline phosphatase test did not come up to our expectations either. Values above 10 Bodansky units, considered to be more in keeping with obstructive

than with hepatocellular jaundice, were encountered in only 16 cases in a group of 21 patients with neoplastic obstruction. In a recent analysis of hepatic tests commonly used in the differential diagnosis of jaundice, Ricketts<sup>12</sup> found that serum alkaline phosphatase values overlapped considerably in obstructive and parenchymatous jaundice, only the values above 30 Bodansky units being found exclusively in the former.

The above evidence can be summarized by stating that, in arriving at the correct diagnosis, the determinations of serum prothrombin time were of no value, and serum proteins, serum cholesterol, and alkaline phosphatase of limited value. Thymol turbidity and cephalin cholesterol flocculation were more helpful. Still, the examination of liver biopsy proved superior to the combined results of thymol turbidity, cephalin flocculation and serum alkaline phosphatase determinations. It is also of interest to note that a diagnostic biopsy of the liver could be secured as early as within one week of the onset of jaundice. This occurred in a few patients who became icteric after admission into the hospital and therefore had a precisely known duration of jaundice prior to biopsy.

An interesting feature of the liver biopsy was the early appearance of the reactive periportal and perilobular fibrosis in some patients. Roholm and Krarup<sup>7</sup> found that in their cases with duration of jaundice of from seven to 110 days the increase in connective tissue was "not a typical feature of this picture; still, rather often there is a slight proliferation of connective tissue in the portal spaces." In the group of cases with longer duration of jaundice (from 180 to 370 days), the same investigators found that "a characteristic feature is the considerable development of connective tissue, so that it will be proper to speak of a veritable cirrhosis, or more neutrally, fibrosis." They concluded: "Thus the occlusion of the bile passages has to persist for a considerable length of time before the cholestatic fibrosis develops." In the series of cases of extrahepatic biliary obstruction studied by Weisbrod, Schiff, Gall, Cleveland and Berman,<sup>8</sup> the duration of jaundice at the time of liver biopsy ranged for from two to 96 weeks. The authors observed that "only in cases of long standing and considerable severity is there active periportal fibrosis and even at its maximum this retains an extra-lobular position and never appears to produce the nodulation which is experienced with the more common forms of cirrhosis." Apparently the two groups of workers above quoted agreed that prolonged duration of obstruction was necessary to produce fibrosis, but differed in their observations as to the extent of this process. Thus Roholm and Krarup,<sup>7</sup> in support of their conclusion that "it will be proper to speak of a veritable cirrhosis," state: "The connective tissue formation is irregular. Streaks of new-formed connective tissue extend out into the liver parenchyma, coming most often from the portal spaces, effacing the lobular structure. . . . The parenchymal cells are shattered more or less by fine or more coarse streaks of connective tissue, so that the trabecular structure is abolished to a

large extent." In addition, ductal proliferation and inflammatory reaction were noted in the connective tissue areas.

We had occasion to observe somewhat more rapid development of reactive fibrosis. In case 11 (neoplastic obstruction) the first needle biopsy of the liver was performed two weeks after the patient first noticed jaundice. Bile thrombi in the intralobular biliary canaliculi were in evidence, the



FIG. 1. Case 12. Needle liver biopsy  $4\frac{1}{2}$  weeks after the onset of jaundice. Note beginning periportal fibrosis. Van Gieson's stain.  $\times 90$ .

lobules being otherwise not remarkable, except for some bile staining. The operation was unfortunately delayed. The second needle biopsy, done 17 days later (about four and one-half weeks after the onset of jaundice) showed, in addition to bile plugs in biliary canaliculi and precipitated bile in the portal ductules, some fibrosis radiating from the portal triad and extending along the perilobular space, beginning to encircle the liver lobule (figure 1). Eight days later the third biopsy performed at the time of

operation (practically six weeks after the onset of jaundice) showed fibrous tissue bridging portal triads (figure 2). However, the last two biopsies were not comparable, inasmuch as the one obtained surgically represented a wedge of tissue not more than 1 cm. in depth. Therefore an allowance must be made for normal subcapsular variation in lobular configuration; slight localized fibrosis is not uncommon in portions of the liver immediately

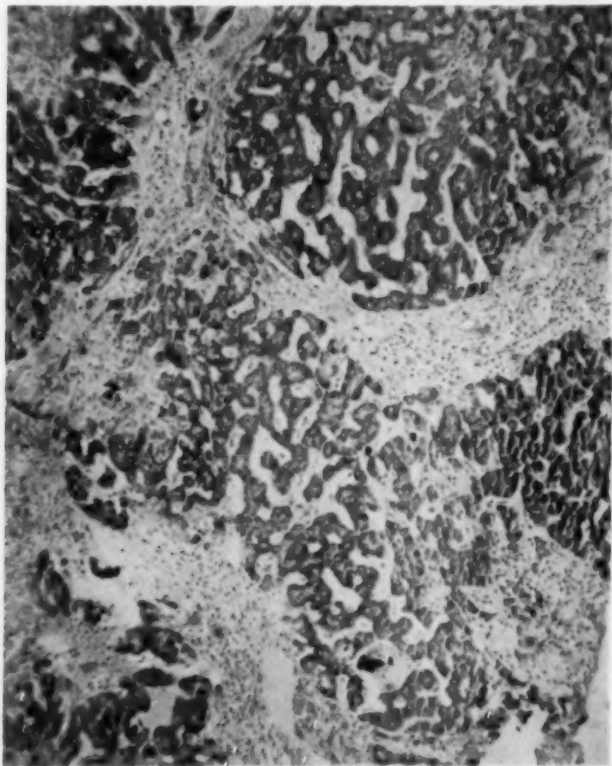


FIG. 2. Case 12. Surgical biopsy of the liver 6 weeks after the onset of jaundice. Periportal fibrosis encircling the liver lobule. Periodic acid Schiff stain.

underlying the capsule. Although needle biopsy of the liver well reflects diffuse hepatic alterations such as occur in infectious hepatitis and fatty metamorphosis, it must not be considered to be equally representative of fibrotic changes, because of its diminutiveness. Therefore the possibility exists that at the time of the first biopsy performed on this patient some periportal fibrosis was already present, even if not apparent in the obtained specimen, and that it was thus unrelated to the biliary obstruction. The

patient was known not to be an alcoholic. In fact, he was a teetotaler, as was ascertained not only through direct questioning (which in this respect frequently elicits notoriously unreliable information), but also on the basis of our evaluation of his personality and the testimony of people who knew him well. Neither was there any history suggestive of infectious hepatitis in the past. In case 13 (carcinoma of the head of the pancreas) there was

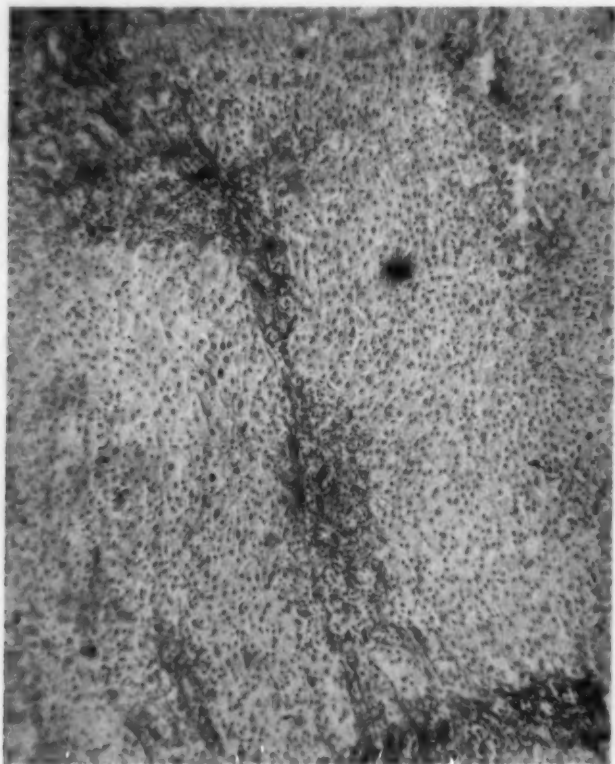


FIG. 3. Case 14. Needle liver biopsy 5 weeks after the onset of jaundice. Note bridging of the portal spaces. Van Gieson's stain.  $\times 90$ .

clinical evidence of cholangitis complicating biliary obstruction. The patient gave a history of chills and fever lasting several weeks before entry, and in the hospital was seen to have a Charcot type of fever. The biopsy of the liver, obtained after five weeks of jaundice, demonstrated fibrous strands bridging portal triads, in addition to numerous bile plugs in the biliary canaliculi and an inflammatory exudate in the portal spaces containing, among other cells, polymorphonuclear leukocytes (figure 3). How-



ever, in this case there was also a history of jaundice of brief duration, of undetermined causation and accompanied by pruritus, about a year before the onset of the present illness. Also, moderate drinking of alcoholic beverages was suspected, although the patient denied it. In case 14 (calculous obstruction) a somewhat similar process, but of milder degree, was observed in the liver biopsy. The latter was obtained after jaundice had lasted for about four months. The patient was not an alcoholic, and gave good nutritional history. Thus, periportal fibrosis may develop rather early in the face of extrahepatic obstruction. In our series the longest duration of jaundice prior to the time of liver biopsy was 16 weeks. In another case it was 12 weeks, and in all remaining 26 patients not over six weeks.

#### SUMMARY

Needle biopsies of the liver were obtained from 28 patients with extrahepatic biliary obstruction due to common duct stone, stricture of the common duct and neoplasm. The results of liver biopsies were compared with those of a battery of hepatic tests. The examination of liver biopsy specimens proved to be much more helpful in arriving at a diagnosis of obstructive jaundice than the combined results of cephalin cholesterol flocculation, thymol turbidity and serum alkaline phosphatase determinations. Moreover, a diagnostic biopsy of the liver could be obtained as early as within one week of the onset of jaundice. Needless to say, a procedure resulting in a definitive diagnosis at the earliest possible moment is of inestimable value.

The early development of beginning periportal fibrosis was demonstrated by liver biopsy in some cases within only a few weeks of the onset of jaundice.

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## MASS SCREENING FOR LOWERED GLUCOSE TOLERANCE \*

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THE decreasing incidence of the infectious diseases with a steadily aging population has focused the attention of the professional workers particularly interested in the health of our nation on the degenerative diseases commonly encountered in older age groups. It has been stated that over one-half of the deaths in the country today are caused by these so-called "chronic diseases."<sup>1</sup> One of these under attack is diabetes mellitus. The importance of early diagnosis and treatment in this disease has been repeatedly emphasized.<sup>2, 3, 4, 5</sup> The rôle played by the Department of Public Health as an effective agency to aid with this problem has been stressed,<sup>6</sup> and under this impetus the Georgia Department of Public Health, in coöperation with the State and local medical societies and the United States Public Health Service, embarked on a program of diabetes case finding in 1950.

### METHOD OF PROCEDURE

Since 1945 the Georgia Department of Public Health has tested over 1,250,000 persons in a Voluntary Multiple Healthtest Program including a chest x-ray and a serologic test for syphilis,<sup>7, 8</sup> so the incorporation of a blood sugar test in 1950 was relatively easy. The Anthrone method of sugar analysis was utilized, the technic of which has been reported previously.<sup>9</sup> Initially, a single uncontrolled blood sugar determination was the entire test for abnormal carbohydrate metabolism. Follow-up examinations by private physicians on suspects referred to them made it apparent that too many individuals with transient or insignificant hyperglycemia were being referred. A modified glucose tolerance test as recommended by the medical society was added to the screening procedure where indicated. This procedure gives to private physicians practicing in rural areas with limited laboratory facilities an added laboratory aid in their armamentarium against diabetes. Urinalysis was included in the tolerance test procedure as an added convenience to the physicians. The criteria used thereafter have been on the basis of this follow-up glucose tolerance test, and the results we are presenting here are the results of this study.

The procedure utilized is simple and has been previously described.<sup>11</sup> A person is brought through the testing line and is asked if he has eaten within two hours, and a blood specimen is taken. Using values slightly higher than those set by the American Diabetes Association, with consideration of

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prior carbohydrate intake (table 1), the persons with blood sugar values above "normal" are referred for their follow-up tolerance tests. Each is asked to report in a fasting state to the testing station, where he is given approximately 100 gm. of glucose in a glass of water and blood specimens are drawn at 45 minutes and two hours after ingestion. Urinalyses are also performed simultaneously with the blood collections. Each person is then classified as having (1) normal blood test, (2) borderline blood test,

TABLE I  
Primary Screening Level for Lowered Glucose Tolerance

When screening blood sugar level is:	Disposition
160 mg. % or over	Referred
120-159 mg. %—No prior food intake	Referred
120-159 mg. %—With prior food intake	Normal
Below 120 mg. %	Normal*

\* Admittedly, a number of mild diabetics have normal fasting blood sugar and therefore some of these may be missed by use of this standard. The answer would be a tolerance test on every person. However, the present method requires only one visit and very few minutes of a person's time to take the primary tests, while over two hours would be required for a tolerance test.

or (3) abnormal blood test on the basis shown in table 2. The borderline and abnormal cases are referred to their private physicians with the report of the test, for diagnosis and, if indicated, for treatment of the cause of the defective carbohydrate utilization. Persons showing glycosuria with or without hyperglycemia are also referred to their private physicians for diagnosis. The Health Department itself makes no diagnoses of diabetes from these tests, and results should be considered in this light. Persons who

TABLE II  
Classification of Suspects on Glucose Tolerance Test

Classification	Blood Sugar Level	
	45 min.	2 hours
Abnormal		Above 160 mg. %
Borderline	Above 160 mg. %	Below 160 mg. %
Normal	Below 160 mg. %	Below 160 mg. %

give a history of previously diagnosed diabetes are given a primary screening test but are not referred back for the confirmatory tolerance test. In order to establish a clinical follow-up on all referred persons, a mimeographed sheet containing a check list of known causes of hyperglycemia is forwarded with the test results to the person's private physician. The physician is requested to mail the sheet back to the Health Department after checking his diagnosis as to the cause of the abnormal carbohydrate metabolism. The results of this phase of the program will be reported in a later paper.

## RESULTS

Since April, 1950, 546,000 persons have voluntarily submitted to a screening procedure for abnormal carbohydrate metabolism. Of these, 235,000 were tested by a single uncontrolled blood sugar determination and were reported previously<sup>10</sup>; 69,549 additional persons were tested in late

1950 and early 1951 by a glucose tolerance test, but the initial screening levels appeared to be too high. For this reason our present analysis includes only 241,457 persons surveyed where follow-up glucose tolerance tests were administered to all suspects and individuals were classified as normal, abnormal or borderline on the basis of corrected criteria. An additional 6,719 persons had incomplete examinations and are not included in this report. Table 3 classifies those referred to physicians (abnormals, borderlines and previously known diabetics) in 10 year age groups and gives the prevalence rates by color and sex.

Of these 241,457 persons receiving completed tests, 4,524 (or 1.87 per cent) were referred to their private physicians as showing abnormal or borderline carbohydrate metabolism; of those referred, only 415 (or 9 per cent) gave a history of previously known diabetes.

TABLE III

Analysis of Results of Mass Screening for Lowered Glucose Tolerance by Sex, Age and Race

Age	No. Tested	No. Referred to Physicians	Prevalence Rate in Per Cent				
			Total	Negro Female	Negro Male	White Male	White Female
0-19	94,648	391	0.4	.36	.53	.37	.40
20-29	36,579	239	0.6	.69	.73	.72	.53
30-39	40,349	617	1.59	2.41	1.19	1.57	1.20
40-49	31,891	976	3.29	5.09	2.87	2.82	2.4
50-59	20,027	1,061	5.39	7.56	4.02	4.98	5.01
60-69	12,463	821	6.70	8.98	5.47	6.23	6.19
70-Above	5,500	407	7.38	8.76	5.32	8.05	7.29
All Ages	241,457	4,512	1.87	2.28	1.49	2.00	1.73

There were 6,801 persons, exclusive of known diabetics, who had abnormal primary screening tests, but on follow-up tolerance tests one third were found to have normal sugar tolerance.

The correlation between analytic findings on urine specimens taken 45 minutes and two hours after ingestion of glucose and blood sugar tolerance test results illustrates the variability of the renal threshold for sugar in different people; 20 per cent of those persons having abnormal glucose tolerance blood tests had no glycosuria; 42 per cent of the persons showing borderline blood tolerance tests had no glycosuria. On the other hand, 3 per cent of the persons tested for urine sugar showed a urine and blood picture as follows: glycosuria of 1 per cent or higher, but a normal blood sugar tolerance. In one series of tests, fasting blood sugars were obtained prior to the glucose tolerance test; 997 persons had either borderline or abnormal glucose tolerance tests, yet 637 (or 80.3 per cent) had normal fasting blood sugars. These findings confirm the observations of others that urine sugar tests are much less effective than blood sugar tests as a diabetes case finding procedure, and that a fasting blood sugar is inadequate as a means for detecting lowered glucose tolerance.

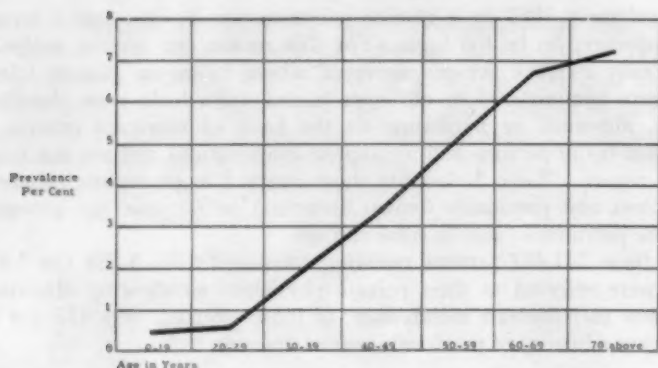


FIG. 1. Prevalence of lowered glucose tolerance in 241,457 persons tested in a mass screening survey.

Analysis of reports of these people with abnormal carbohydrate metabolism as to age, sex and race shows (figure 1) that the prevalence in the general population increases almost on a straight line with the increase of age, with the highest incidence (7.38 per cent) in those over 70 years of age. However, when considering the actual number of people referred, we find that one-half of the total number referred are under 50 years of age, and that 8.6 per cent are under 20 years of age.

When race and sex are considered (figure 2), we find that there is a definitely higher prevalence of abnormal carbohydrate metabolism in the Negro female and a lower prevalence in the Negro male. This difference is most pronounced among the ones classified as abnormal. The difference

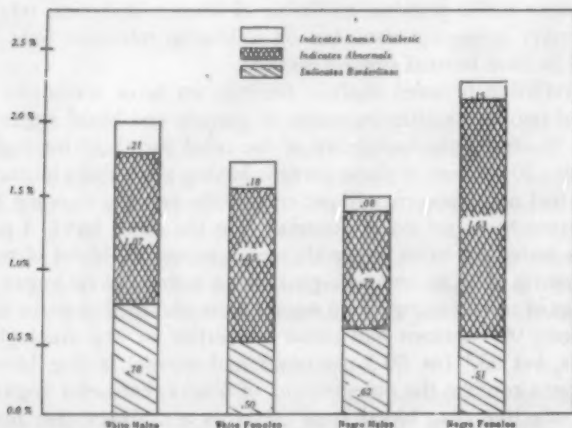


FIG. 2. Analysis of diabetes case findings by race and sex. Breakdown showing abnormal and borderlines, as defined in the text, and known diabetics with prevalence in per cent.



is lost in an over-all comparison between the races, i.e., the prevalence in Negroes of both sexes is 1.88 per cent vs. 1.86 per cent in whites. The aggregate incidence of abnormal tolerance curves in colored and white females is slightly higher than in the combined males, 2.0 per cent vs. 1.74 per cent, but this is apparently produced by the unusually high rate in the colored females. An unexpected finding is the higher rate in the white male as compared to the white female, 2.0 per cent vs. 1.73 per cent. However, the difference may be more apparent than real, since the increased incidence is entirely in the group classified as "borderline," plus a slightly higher known diabetic rate.

#### COMMENTS

It is believed that these surveys have collected more information about the blood sugar findings in a cross section of a population voluntarily submitting to screening than has ever been gathered previously in as large a group. These findings are summarized here because it is believed that this large volume of factual information should be made available for analysis by all. The statistics are conservative, for the screening levels were purposely high, and it was not possible to do tolerance tests on all persons.

It is hoped that presentation of the results of the diabetes case finding study in the State of Georgia will stimulate similar programs elsewhere. It should be emphasized, however, that the mechanical testing of blood sugars by any organization is in itself only the initial step in the right direction. The population involved should be educated regarding diabetes so that they can accept the responsibility of continuing the search for hidden disease in themselves and in their families with the full coöperation of their private physicians.

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## CLINICAL CORRELATION OF PRETIBIAL MYXEDEMA WITH MALIGNANT EXOPHTHALMOS\*

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ALMOST 100 patients with localized pretibial myxedema had been reported by 1949.<sup>1</sup> The association of these lesions with exophthalmic goiter has been noted as early as 1930.<sup>2</sup> Curtis, Cawley and Johnwick<sup>3</sup> in 1949 reported the association of malignant exophthalmos and pretibial myxedema in three cases studied by them and in seven others known or reported previously. These authors also first emphasized<sup>3</sup> that both the malignant exophthalmos and the localized myxedema might be due to the same factor, i.e., a local effect of thyroid-stimulating hormone, T.S.H., in the extraocular tissues and in the subcutaneous areas of the anterior lower leg. Review of the literature reveals no report of a systematic effort to determine the incidence of localized pretibial myxedema in patients suffering from malignant exophthalmos. This paper reports an attempt to find this incidence and also to determine from clinical data on exophthalmic patients why some who are suffering from exophthalmos have this associated complication, while others do not. Lastly, certain little-known clinical features of this association will be stressed.

### METHOD

The author was following a series of patients with malignant exophthalmos when, in July, 1952, it was decided to scrutinize the shin area of each of these patients for evidence of localized myxedema. All patients previously had presented two or more eye signs of malignant exophthalmos. These signs have been listed<sup>4,5</sup> as increasing Hertel exophthalmometer measurements, plus one or more of the following: lid edema, bulbar conjunctival edema, limitation of extraocular muscle movement of the eyes, inability to close the eyes, and corneal ulceration. Details were also reported<sup>4,5</sup> regarding determination of exophthalmometer measurements, palpebral fissure measurement with eyes open and "closed," tonometer tension, and estimation of lid and bulbar conjunctival edema, corneal ulceration, and limitation of extraocular muscle movements. It should be stressed that, at the time of the specific examination of these patients for the presence of pretibial myxedema, many patients already had shown improvement of their exophthalmos.

This report analyzes the findings in the first 28 patients with malignant exophthalmos carefully examined for the presence of pretibial myxedema

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from July, 1952, through January, 1953. Biopsy was done in four of seven patients who were found to have clinical evidence of pretibial myxedema. The diagnosis of each case was confirmed by one or more members of our Dermatology Department under the direction of Dr. A. C. Curtis. Statistical analyses of data comparing the two groups of exophthalmos patients, i.e., those with pretibial myxedema and those without pretibial myxedema, were made by Benjamin J. Darsky, M.A.\*

After this survey of consecutive exophthalmos patients in the out-patient department, the author examined all records of patients in the University Hospital from July 1, 1934, to December 31, 1952, with diagnosis coded under myxedema, including pretibial myxedema. These 401 records were examined to determine the incidence of pretibial myxedema not associated with exophthalmos.

### RESULTS AND DISCUSSION

Table 1 summarizes the clinical data on 28 exophthalmic patients with and without localized pretibial myxedema at the time they were examined specifically for the presence of this edema. It should be emphasized that in all of these patients, malignant exophthalmos as previously defined by this author<sup>4</sup> was present or had been present. Careful examination of this table will show that some of these patients had few remaining signs of malignant exophthalmos at the time of this examination.

Seven (or one fourth) of the 28 patients with past or present malignant exophthalmos were found to have localized pretibial myxedema. It is likely that no instance of pretibial myxedema in these 28 patients with exophthalmos was missed, since biopsy was made of the only other visible pretibial skin lesions, occurring in two patients. The dermatologist had suspected neurodermatitis in one patient and stasic dermatitis in the other. Biopsy results in these two patients were compatible with the dermatologist's diagnosis and showed no evidence of pretibial myxedema.

In general, analysis of clinical data in the two groups of patients, i.e., exophthalmic patients with pretibial myxedema and exophthalmic patients without pretibial myxedema, revealed no significant difference between the two groups other than the pretibial myxedema.

*Sex:* It was logical to look for a difference in sex distribution in the two groups (table 1) for the following reasons: Although exophthalmic goiter occurs four times more commonly in females than in males,<sup>6</sup> serious exophthalmos reportedly occurs in a higher percentage of males.<sup>7</sup> If both pretibial myxedema and malignant exophthalmos are due to increased local effect of pituitary thyroid-stimulating hormone, pretibial myxedema might, like malignant exophthalmos, also occur more commonly in males than in females. Furthermore, estrogens have been used enthusiastically by a few

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TABLE I

A Summary of Clinical Data on 28 Exophthalmic Patients with and without Localized Pretibial Myxedema at the Time They Were Examined Specifically for the Presence of This Edema. Several patients had shown minimal to marked improvement in their exophthalmos at the time of this examination.

Patient	Age	Sex	Pre-tibial Myxedema	Duration of Exophthalmos	Thyrotoxicosis	Type of Treatment of Thyroid Disease	Exophthalmometer Measurements	Lid Edema	Conjunctival Edema	Corneal Ulceration	Palpebral Features in mm.	Extracocular Muscle Pulley	B.M.R.	Basal Pulse Rate	Serum Cholesterol, mg. %	Biopsy Obtained
L. F.	47	F		77 months	Formerly present	Thyroidectomy, 1st, desiccated thyroid	19.5/22	++/++	0/+	0/0	13/14 2/2	Diplopia	-15	72	170	
S. G.	53	F		56 months	Present	Thyroidectomy, 1st, desiccated thyroid	17.5/18.5	0/0	0/0	0/0	11/13 0/0	None	+1	64	201	
M. G.	29	M		50 months	Formerly present	Propylthiouracil, 1st, thyroid, x-ray to pituitary	24/22	++/++	+0	+/++	16/16 2/3	Limitation of upward gaze	+4	70	147	
M. H.	36	F		54 months	Formerly present	Thyroidectomy, 1st, x-ray to pituitary, stilbestrol	22/23	++/++	+/+	+0	19/19	Limitation of horizontal and upward gaze	+7	56		
L. H.	35	F		12 months	Not present	X-ray to pituitary	25/26	++/++	+/+	+0	17/17 2/2	None	+6	80	212	
H. J.	61	M		18 months	Formerly present	Thyroidectomy, desiccated thyroid, x-ray to pituitary	17/17	++/++	0/0	0/0	14/14 1/2	None	-29	68	332	
M. L.	34	F	Present	48 months	Formerly present	Propylthiouracil, desiccated thyroid, x-ray to pituitary	19.5/21.5	++/+	0/+	0/0	10/10	None	+3	76	163	No
M. M.	44	F	Present	36 months	Formerly present	Thyroidectomy, desiccated thyroid	26.5/25.5	++/++	-	0/0	12/11	None	-21	70	164	Yes
R. M.	34	F		12 months	Formerly present	1st, desiccated thyroid	20.5/22.5	+/+	+0	0/0	11/11 2/3	None	-19	60	218	
E. M.	38	F		84 months	Formerly present	Thyroidectomy, para-hydroxypropio-phenone, desiccated thyroid, diethylstilbestrol	18.5/18	+/+	+/+	0/0	11/12	Diplopia	-9	-	260	
G. M.	71	M	Present	56 months	Formerly present	Propylthiouracil, desiccated thyroid	22/23	++/++	0/+	0/0	-	Marked	+3	64	185	No
C. P.	35	F		84 months	Not present	Desiccated thyroid, Lugol's, x-ray to pituitary	16/17	0/0	+/++	0/0	-	None	-12	72	347	
A. P.	43	F		36 months	Formerly present	Propylthiouracil, 1st, desiccated thyroid, para-hydroxypropio-phenone	23/23	++/+	0/0	+0	16/16	None	-	-	320	

TABLE I—Continued

Patient	Age	Sex	Pre-thyroidal edema	Duration of Exophthalmos	Thyrotoxicosis	Type of Treatment of Thyroid Disease	Exophthalmometer Measurements	Lid Edema	Conjunctival Edema	Corneal Ulceration	Palpebral Fissures in mm.	Extraocular Muscle Palsy	B.M.R.	Basal Pulse Rate	Serum Cholesterol, mg. %	Biopsy Obtained
M. R.	33	F	Present	54 months	Formerly present	Thyroidectomy, desiccated thyroid, 1 gm, x-ray to pituitary gland, 1 gm	23.5/24	++/++	0/+	0/0	Open 14/14	None	— 1	72	150	Yes
E. R.	36	F		156 months	Not present	Lugol's, thyroidectomy, 1 gm, x-ray to pituitary gland, 1 gm	21.5/22.5	++++	+/+	+/0	15/13	None	— 6	64	197	
R. S.	27	F		72 months	Formerly present	Propylthiouracil, 1 gm	20/20.5	0/0	0/0	0/0	16/16	None	— 18	—	389	
C. S.	55	M		54 months	Formerly present	Lugol's, thyroidectomy, 1 gm	24/29	++++	++++	0/0	9/11	Moderate O.S.	—	—	258	
A. H.	52	F	Present	128 months	Formerly present	Lugol's, thyroidectomy, 1 gm	14/16	0/0	0/0	0/0	11/11	None	— 13	64	224	Yes
C. M.	49	M		72 months	Formerly present	Propylthiouracil, 1 gm	22/21	0/0	0/0	0/0	1/0	None	— 17	80	209	
L. K.	28	M		28 months	Not present	Desiccated thyroid, x-ray to pituitary gland, 1 gm	21/20	+/+	—	+/0	12/10	None	— 9	72	205	
H. R.	54	M	Present	17 months	Not present	Desiccated thyroid, x-ray to pituitary gland, 1 gm	25/18	++++	0/0	+/0	12/7	Marked O.D.	+ 5	100	222	No
M. V.	51	F		18 months	Formerly present	Lugol's, thyroidectomy, 1 gm, x-ray to pituitary gland, 1 gm	20/21	++++	++++	0/0	9/10	Minimal	+ 4	60	210	
E. S.	34	F	Present	36 months	Present	Desiccated thyroid, x-ray, 1 gm, x-ray to pituitary gland, 1 gm	23.5/25	++++	++++	0/+	12/13	Minimal	+ 9	72	153	Yes
J. C.		M		84 months	Formerly present	Lugol's, propylthiouracil, 1 gm, x-ray to pituitary gland, 1 gm	27/27	++++	++++	0/0	14/14	Moderate	— 6	80	255	
G. B.	49	F		42 months	Present	Thyroidectomy, 1 gm	23/25	+/+	+/+	0/0	16/16	Minimal	— 1	60	301	
N. K.	43	F		40 months	Formerly present	x-ray	27/26	+/0	+/0	0/0	13/11	None	— 4	64	204	
F. H.	37	F		127 months	Formerly present	4 thyroidectomies, 1 gm	18/18	+/0	+/0	+/0	12/10	None	— 4	74	—	
K. F.	48	F		84 months	Formerly present	Propylthiouracil, 1 gm	21/21.5	++++	+/+	0/0	11/10	Diplopia	— 6	—	263	

authors to treat all three diseases—exophthalmic goiter, malignant exophthalmos and pretibial myxedema. However, no significant difference in sex distribution between the two groups was apparent. Of the total 28 patients with malignant exophthalmos, 20 were females and eight were males. Twenty-five per cent of each sex had pretibial myxedema.



FIG. 1A. Case 1. Appearance of eyes.



FIG. 1B. Case 1. Appearance of legs.

*Age:* Mulvaney<sup>7</sup> has noted that patients with uncomplicated exophthalmic goiter are relatively young as contrasted with patients with serious exophthalmos. Generally, the incidence of exophthalmos is higher in thyrotoxicosis of long duration than in thyrotoxicosis of short duration. It seemed logical, therefore, to look for pretibial myxedema in older persons



and as a second complication of thyrotoxicosis that might come even later than exophthalmos in the course of thyrotoxicosis. It was found not to be true, however, that exophthalmic patients without pretibial myxedema were younger or had thyrotoxicosis or exophthalmos of shorter duration than the seven patients with the additional complication of pretibial myxedema. The average age of all exophthalmos patients was 42.8 years, the youngest

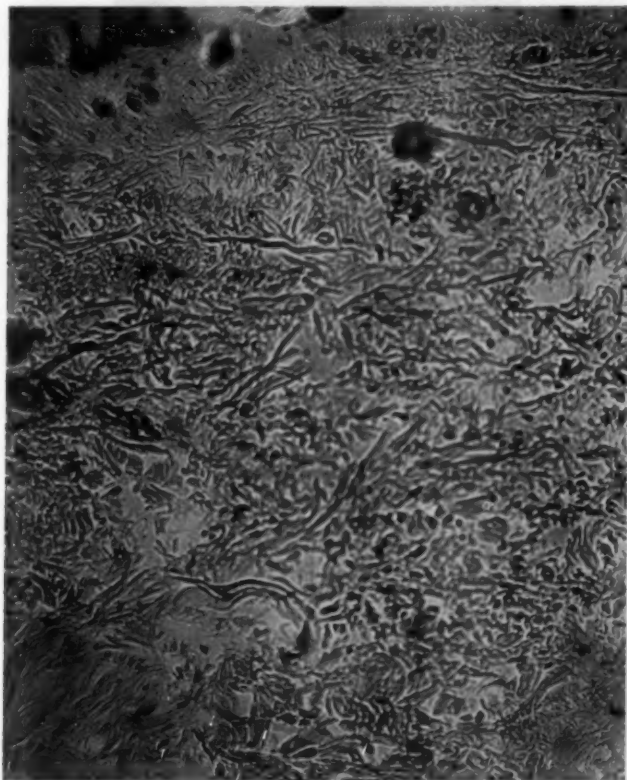


FIG. 1C. Case 1. Biopsy of pretibial myxedema area. Pathologist's report: "Changes in the dermis are compatible with a mild degree of localized myxedema."

patient being 27 years and the oldest, 71 years of age (table 1). The average, minimal and maximal ages of patients with pretibial edema were 46, 33 and 71 years, respectively. Average, minimal and maximal ages of patients with no pretibial myxedema were 42, 27 and 61 years, respectively. It was of interest that all seven patients with exophthalmos and pretibial myxedema developed symptoms of thyrotoxicosis before pretibial



FIG. 2A. Case 2. Appearance of eyes.



FIG. 2B. Case 2. Appearance of legs.

edema was noted. It was also interesting that pretibial edema usually was noted after the development of exophthalmos. Data on the duration of exophthalmos in years (table 1) in the seven patients with associated pretibial myxedema and in the 21 patients without associated myxedema were submitted to t-tests. These showed that the "differences between means could

be accounted for on the basis of random variations in more than five times out of a hundred. Therefore, the two groups could not be considered to represent two different populations."

*Thyrotoxicosis at Time of Examination:* It seemed advisable to rule out the possibility that at the time of their examination the seven patients with



FIG. 3A. Case 3. Appearance of eyes.



FIG. 3B. Case 3. Appearance of legs.

pretibial myxedema associated with malignant exophthalmos had more or less thyrotoxicosis than those exophthalmic patients without associated pretibial edema. Data obtained on this point included presence or absence of thyrotoxicosis by history, values of basal metabolic rate, basal pulse rate, and serum cholesterol determinations (table 1). No significant difference between the group of patients with pretibial myxedema and the group of

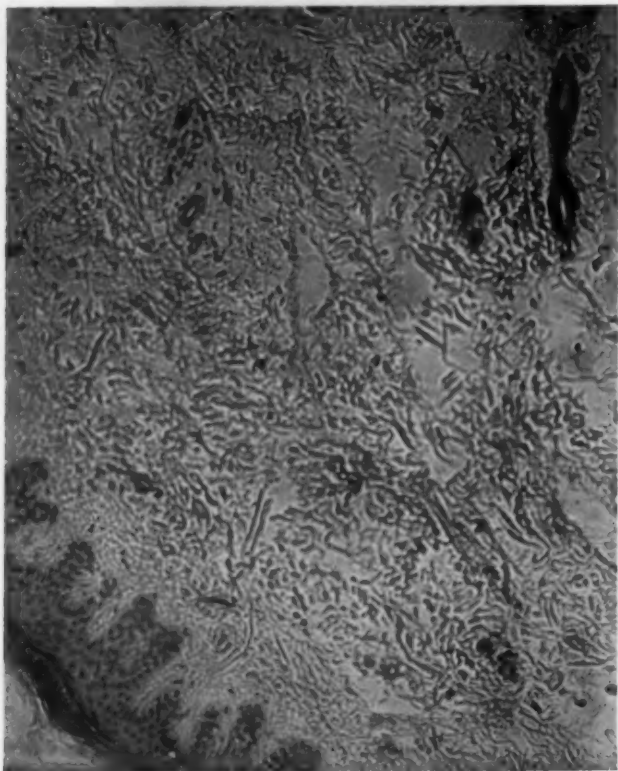


FIG. 3C. Case 3. Biopsy of pretibial myxedema area. Pathologist's report: "Minimal evidence of localized myxedema in the dermis."

patients without pretibial myxedema was found in regard to the above-noted factors.

*Previous Treatment of Thyrotoxicosis and Exophthalmos:* Analysis of the type of treatment of the thyrotoxicosis and exophthalmos prior to or at the time of examination of the shins for myxedema disclosed no tendency for one type of treatment to precede the development of pretibial myxedema significantly more often than another (table 1). Forms of therapy in-

cluded Lugol's solution of iodine, antithyroid drugs, thyroidectomy, radioactive iodine, desiccated thyroid, parahydroxypropiphenone, and X-irradiation of the pituitary.



FIG. 4A. Case 4. Appearance of eyes.

*Severity of Exophthalmos:* If both malignant exophthalmos and pretibial myxedema are caused by local effect of thyroid-stimulating hormone, it is logical to expect pretibial myxedema to occur more commonly in the presence



FIG. 4B. Case 4. Appearance of legs.

of marked malignant exophthalmos than in the presence of exophthalmos of mild degree. Such was not the case. Analysis of data in exophthalmic patients with pretibial myxedema as compared to exophthalmic patients without myxedema showed that no significant difference between the two

groups existed in the degree of exophthalmos (table 1). The factors checked to estimate severity of exophthalmos were the following: degree of exophthalmos in millimeters; lid edema, conjunctival edema, corneal ulceration, and extraocular muscle palsy graded 1 plus to 4 plus; and distance between upper and lower lids measured in millimeters with eyes open and with eyes "closed."

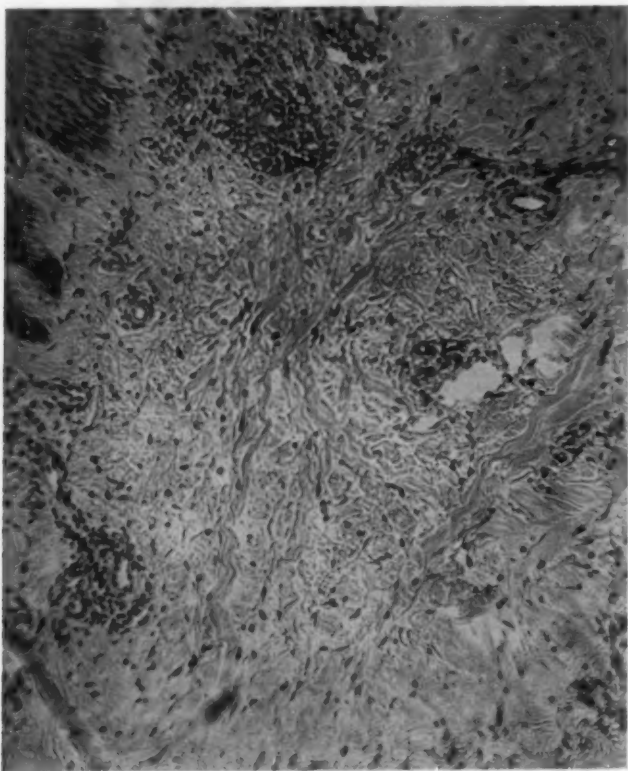


FIG. 4C. Case 4. Biopsy of pretibial myxedema area. Pathologist's report: "Edematous change in dermis is interpreted as diagnostic of myxedema."

*Pretibial Myxedema Patients Without Exophthalmos as the Chief Complaint:* Review of the records of 401 patients with diagnoses coded under myxedema in an attempt to find the incidence of pretibial myxedema not associated with exophthalmos revealed four additional patients with pretibial myxedema. These patients all had biopsy proof of pretibial myxedema. One of these three patients noted that her lesions appeared coincident with the appearance of symptoms of exophthalmic goiter; two





FIG. 5A. Case 5. Appearance of eyes.



FIG. 5B. Case 5. Appearance of legs.

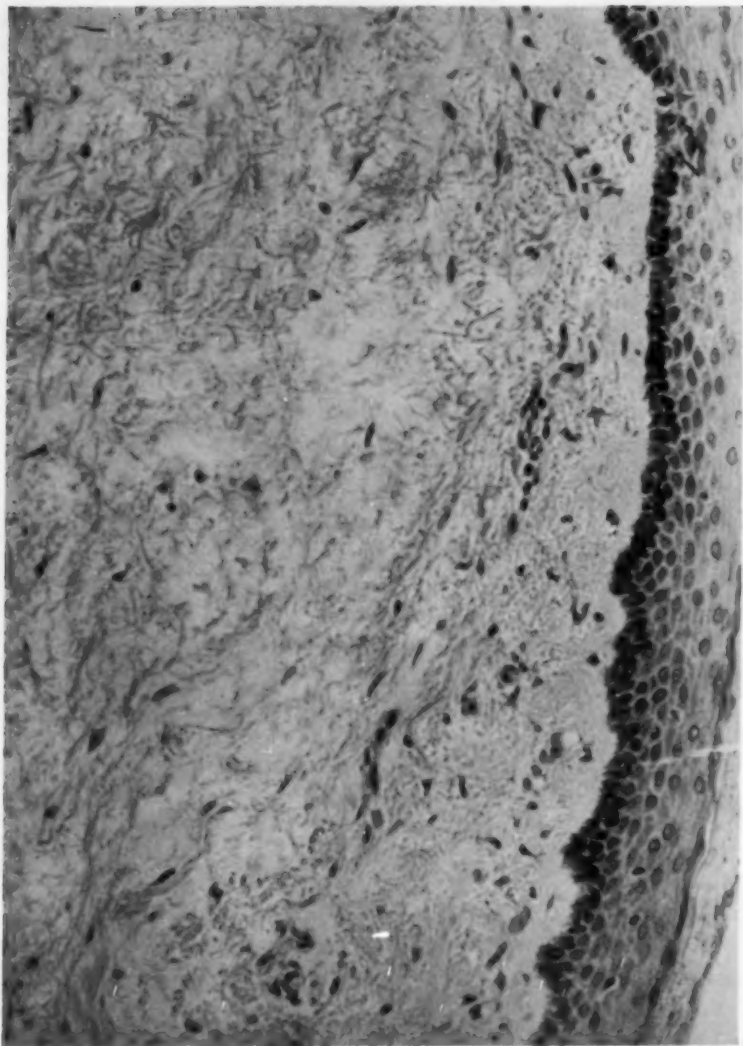


FIG. 5C. Case 5. Biopsy of pretibial myxedema area. Pathologist's report: "Mucoid degeneration in the corium which is marked in degree in some areas. Occasional small focus of lymphocytes about sweat glands. The changes are compatible with myxedema."

patients noted this complication after thyroidectomy for exophthalmic goiter; and the fourth patient, after two years of inadequate antithyroid drug therapy for exophthalmic goiter. All had some increased protrusion of their eyes as measured by the Hertel exophthalmometer.

## NOTEWORTHY FEATURES OF PRETIBIAL MYXEDEMA

A few clinical features of these patients with pretibial myxedema are of interest and have not been stressed before in the literature. Frequently, although not invariably, the longer the pretibial myxedema persists, the more extensive it becomes. Figures 1 to 5 show face and legs of five of the seven patients with malignant exophthalmos and pretibial myxedema, and histology of biopsy specimen from pretibial edema area of four of these patients.\* Note that the first three patients (figures 1, 2, 3) have very small



FIG. 6. Case 6, B. B., a 26 year old woman with congenital torticollis. (A) Appearance of face when first seen at University Hospital, March 29, 1950, with exophthalmic goiter of eight months' duration. No pretibial myxedema was present. (B) July 22, 1953, after continuous thyrotoxicosis in the interim.

areas of localized pretibial myxedema. The patient was not aware of the lesion until it was called to his attention. The last two patients (figures 4, 5) have rather extensive involvement of the shins. The fourth patient (figure 4) was thought to have extensive infection and ulceration in stasis dermatitis until the infection and inflammation were cleared in the hospital. Her pretibial myxedema had apparently been present for two years. The fifth patient (figure 5) had known of her skin lesion for some months. Extensive lesions may develop in as short an interval as two years after the onset of thyrotoxicosis, as illustrated by the following case report.

## CASE REPORT

B. B. was a 26 year old woman with congenital torticollis when first seen in University Hospital by the author on March 29, 1950. She had exophthalmic goiter of eight months' duration. Figure 6a shows her appearance at that time. She had

\* Pathology specimens from the department of C. V. Weller, M.D.

no pretibial myxedema at that time. She was treated with propylthiouracil, but took it intermittently until her reappearance at University Hospital July 22, 1953 (figure 6b). She had suffered continuously from thyrotoxicosis between these two admissions. Now she was found to have extensive pretibial myxedema, as shown in figure 6c, proved by biopsy as in figure 6d.

Treatment of pretibial myxedema was totally ineffective. Five patients developed pretibial myxedema during treatment for their thyrotoxicosis and exophthalmos. Three patients developed pretibial myxedema while receiving desiccated thyroid. None of six patients treated with desiccated thyroid



FIG. 6C. Case 6. Legs, showing pretibial myxedema, July 22, 1953.

for pretibial myxedema for nine, 12, 13, 14 and 24 months, and seven years, respectively, have shown a decrease in their pretibial edema. Of even greater interest is the fact that patient M. M. has shown equivocal decrease in her exophthalmometer measurements from 27 mm. O.U. on October 24, 1950, when she received X-irradiation of the pituitary, to 26.5 mm. O.D. and 25.5 mm. O.S. on December 14, 1951, yet no simultaneous decrease in the extent of her pretibial myxedema has been apparent. Significant recession of exophthalmos was observed in A.H., whose readings decreased from 17 mm. O.D. and 18 mm. O.S. on January 31, 1952, to 14 mm. O.D. and 16 mm. O.S. on November 7, 1952, while on desiccated thyroid and diethylstilbestrol, yet her area of involvement with pretibial myxedema doubled

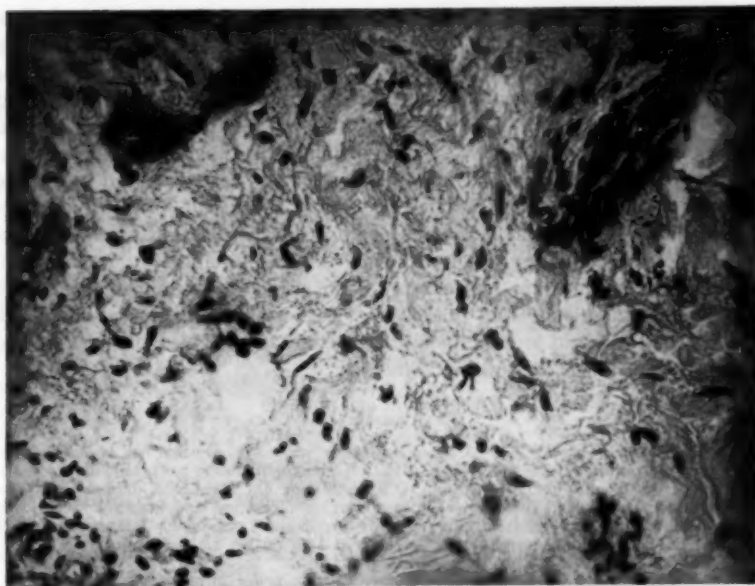


FIG. 6D. Case 6. Skin biopsy of shin, July 27, 1953: "There is a patchy distribution of material resembling connective tissue mucin. While material is scant, this is probably sufficient for a diagnosis of pretibial myxedema."

in size during this same interval. This observation is hard to reconcile with the hypothesis that both exophthalmos and pretibial edema are caused by local effect of one hormone.

#### SUMMARY AND CONCLUSIONS

Twenty-eight patients who had malignant exophthalmos, past or present, as defined by this author, were carefully examined in a six month period for the presence of pretibial myxedema. Seven (or one fourth) of these patients were found to have pretibial myxedema. The diagnosis previously had been missed by the same examiner on six of these same patients before a specific search was made. Biopsy proof was obtained in four of these patients and was not attempted in three. It is unlikely that other instances of pretibial myxedema were missed in the remaining 21 patients with serious exophthalmos, since biopsy of atypical but bilateral shin lesions in two of these patients was negative for pretibial myxedema. Comparison of the two groups, i.e., exophthalmic patients with associated pretibial myxedema and exophthalmic patients without associated pretibial myxedema, showed no difference in regard to sex or age of patients, duration of exophthalmos, presence or absence of thyrotoxicosis, basal metabolic rate, basal pulse rate,

serum cholesterol, type of treatment of thyrotoxicosis, or severity of signs of malignant exophthalmos. Review of 401 records from the files of the University Hospital between 1934 and 1952 coded as myxedema, including pretibial myxedema, revealed four more cases of pretibial myxedema, all associated with exophthalmic goiter. Patients with pretibial myxedema were usually observed to have larger pretibial areas involved by myxedema as duration of the myxedema increased. Patients were observed to develop their lesions while taking desiccated thyroid. No patient showed regression of his lesions on desiccated thyroid therapy for periods up to eight years. One patient showing equivocal regression of exophthalmos following X-irradiation of the pituitary had no regression of pretibial edema. One post-menopausal patient showing unequivocal regression of exophthalmos while on desiccated thyroid and diethylstilbestrol therapy doubled the area of pretibial myxedema during this same interval.

#### ADDENDUM

M. L. returned October 2, 1953, after this paper was written. She had received X-ray therapy to the pituitary region March 20, 1952. Her exophthalmos had gradually decreased since then from 20 mm. O.D. and 23 mm. O.S. to 20 mm. O.U. while off desiccated thyroid. Extraocular muscle palsy, conjunctival edema, corneal ulceration and inability to close the eyes had all cleared during this same time. Her pretibial myxedema had cleared completely from the left leg and had decreased 80 per cent in area on the right leg.

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## GYNECOMASTIA: A REVIEW AND AN ANALYSIS OF 160 CASES \*

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GYNECOMASTIA has been reported as an accompaniment of certain physiologic states and a wide variety of pathologic conditions. It is the purpose of this paper to (1) define gynecomastia, (2) review the theories concerning its etiology, (3) report the data derived from an analysis of 160 cases of gynecomastia, (4) discuss etiologic possibilities suggested by a study of the 160 cases, (5) point out some of the clinical implications of gynecomastia, and (6) suggest a clinical classification of conditions which may be accompanied by gynecomastia.

### DEFINITION OF GYNECOMASTIA

Gynecomastia (derived from two Greek words meaning *woman* and *breast*) implies a circumscribed, potentially reversible enlargement of the male breast which results from a combination of changes in the breast, including a nonencapsulated increase of connective tissue, proliferation of the ducts of the mammary gland, increased vascularity, and infiltration by chronic inflammatory cells.<sup>29, 38, 46, 65</sup> The bulk of the enlargement lies directly under the nipple and areola. Tenderness, a colostrum-like secretion and enlargement of the nipple and areola may or may not be present. Depending on the preponderance of one or the other of the microscopic components, pathologists suggest diagnoses of hormonally induced gynecomastia, fibroadenoma, adenofibroma, adenomyxofibroma and chronic cystic mastitis.<sup>38, 46</sup>

### THEORIES CONCERNING THE ETIOLOGY OF GYNECOMASTIA

Current theories regarding the etiology of gynecomastia can be conveniently grouped for discussion as follows: (a) gynecomastia resulting from the administration of hormones; (b) gynecomastia occurring in conjunction with physiologic processes which are productive of hormonal imbalance, and (c) gynecomastia occurring in conjunction with pathologic states which are productive of hormonal imbalance.

*Gynecomastia Resulting from the Administration of Hormones:* Estrogenic hormones are particularly potent in their ability to produce gynecomastia, and they apparently act directly upon the mammary gland, since it is known that the topical application of these hormones to one gland (in

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both man and animal) will cause growth of the treated nipple and proliferation of the ducts of the treated gland, without affecting the untreated nipple and gland.<sup>29, 38, 41, 65, 66, 69, 71, 74</sup> The lack of response of the mammary glands of pituitectomized animals to topically or parenterally administered estrogen suggests, however, that the pituitary elaborates some agent which makes possible the effect of the administered estrogen.<sup>3, 19, 21, 36, 58</sup> Androgens, such as testosterone and methyl testosterone, may cause enlargement of the male breast when applied topically (experimental animals) or administered parenterally (experimental animals and man).<sup>3, 36, 44, 45, 58, 71, 74</sup> A similar effect may appear after the administration of adrenal cortical extract, desoxycorticosterone acetate and other hormones derived from the cortex of the adrenal gland.<sup>13, 26, 52, 56, 69, 71, 74</sup>

Chorionic gonadotrophin acts by stimulating the testicle (and possibly the adrenal) to produce androgens and estrogens (and cortical hormones) which account for the effects on the mammary gland.<sup>15, 17, 22, 42</sup> A recent study suggests that the primary action of chorionic gonadotrophin is upon the Leydig cells of the testicle, with resulting proliferation of these cells, and excessive elaboration of androgenic and estrogenic hormones.<sup>42</sup>

Pituitary hormones undoubtedly play an important rôle in the production of gynecomastia in certain cases, but the mechanisms involved are exceedingly complex and incompletely understood. Current evidence, derived from animal experiments, suggests three possible modes of action: (1) One or more pituitary hormones (mammogen I, mammogen II) may exert a direct effect on the breast, resulting in gynecomastia. (2) One or more pituitary hormones (adrenocorticotrophin, gonadotrophin) may stimulate other endocrine glands, including the adrenal and testicle, to produce hormones which cause gynecomastia by their effect on the breast. (3) One or more pituitary hormones (growth, thyrotropic) may, by a complex and circuitous route, maintain the breast in such a state that it responds, with the development of gynecomastia, to hormones elaborated by other endocrine glands.<sup>3, 11, 19, 21, 36, 52, 57, 69</sup>

*Gynecomastia Occurring in Conjunction with Physiologic Processes Which Are Productive of Hormonal Imbalance:* The transitory gynecomastia which frequently occurs in newborn infants is probably the result of transplacental passage of circulating hormones from the mother to the fetus before birth, but hormonal changes occurring in the infant immediately after birth have not been definitely excluded.<sup>7, 40, 53</sup>

The gynecomastia of puberty and adolescence (the incidence is higher than 90 per cent) is difficult to explain, because the hormonal changes which occur in the course of this physiologic process are not well understood. Increased amounts of pituitary, adrenal and testicular hormones, as well as an imbalance among these hormones, are thought to produce the gynecomastia, which usually appears at age 11 or 12 or in the early teens, lasts two to four years, and disappears by the late teens or early twenties.<sup>3, 27, 60</sup> Occasionally the breast enlargement may persist into adult life.

*Gynecomastia Occurring in Conjunction with Pathologic States Which Are Productive of Hormonal Imbalance.* Hypertrophy of the adrenal cortex, and hormone secreting tumors (usually carcinomas) of the adrenal cortex, produce gynecomastia by elaborating excessive amounts of adrenal cortical and estrogenic hormones.<sup>29, 48, 54, 59, 63, 66, 70</sup> The effect on the breast is the same as that induced by the parenteral administration of these hormones. The gynecomastia which is occasionally encountered in Addison's disease results from administration of adrenal hormones in treatment of the disease.<sup>19, 29, 68</sup>

Some testicular tumors (chorio-epitheliomas, teratomas) secrete chori-  
onic gonadotrophin, and others (interstitial cell tumors) secrete androgen  
and estrogen, which have the same effect on the breast as if the hormones  
had been administered parenterally.<sup>19, 29, 32, 42, 54, 72</sup>

Surgical removal of the testicle or any disease of the testicle that decreases the number of functioning Leydig cells may be accompanied by gynecomastia.<sup>19, 20, 29, 32, 34, 38, 46</sup> The absence or diminution of testicular androgenic hormone presumably results in a relative excess of estrogenic hormone, which in turn causes the gynecomastia.

Gynecomastia may be associated with atrophy of the testicular tubules in Klinefelter's syndrome (small testicles, atrophy of testicular tubules, azoospermia, morphologic changes of the Leydig cells, normal or slightly decreased 17-ketosteroid excretion, increased urinary excretion of pituitary gonadotrophins, normal secondary sex characteristics, and gynecomastia).<sup>8, 19, 22, 33, 35</sup> It is postulated that inactive seminiferous tubules fail to elaborate an inhibitory hormone (inhibin). The lack of inhibin allows a normal or decreased amount of androgenic hormone to act on breast tissue to produce gynecomastia.<sup>33</sup>

Gynecomastia is frequently encountered in hepatic disease. The liver normally inactivates estrogenic substances. This function may be impaired by liver disease so that there is, in effect, an excess of circulating estrogen similar to that produced by parenteral administration of the same hormone. Liver cell damage by diseases such as cirrhosis, hepatitis and carcinoma may impair this ability of the liver cells to inactivate estrogenic hormones. In addition, dietary deficiencies (protein and vitamin, especially vitamin B) may have a similar effect on the liver without producing demonstrable anatomic change in the liver cells.<sup>5, 6, 14, 16, 24, 26, 28, 30, 31, 39, 51, 55, 60, 61, 62, 63, 70</sup>

Gynecomastia is a frequent manifestation of starvation and malnutrition. The breast often enlarges when the period of deficient nutrition is interrupted by better dietary circumstances.<sup>24, 26, 28, 30, 61, 68</sup> Many theories are offered in explanation of this observation. Decreased ability of the liver to inactivate estrogenic hormones, temporary excesses of adrenal and pituitary hormones, diminished testicular function and unbalanced hormone production head the list of explanations for the gynecomastia of starvation and refeeding.

Gynecomastia has also been reported in patients who were given digitalis

for congestive heart failure. It has been suggested that digitalis may exert an estrogenic effect upon breast tissue because the aglycone fraction of digitalis is similar in structure to some of the steroid hormones.<sup>87</sup> In addition, however, hepatic function may be impaired during congestive heart failure, and the gynecomastia may arise through a mechanism similar to that of the gynecomastia of cirrhosis.<sup>87</sup>

Albright's disease is characterized by the presence of bone cysts, areas of cutaneous hyperpigmentation, and precocious puberty in the female.<sup>1, 2</sup> Hormonal changes in this disorder are not confined to precocious puberty in the female, however, because hyperthyroidism may also occur, males occasionally show mild degree of precocious development, and gynecomastia has been reported as part of the syndrome.<sup>1, 2, 20, 30</sup> It has not been established whether gynecomastia represents an integral part of the disorder or is simply a manifestation of puberty in a male with the syndrome.

The enlargement of the breast which occurs in true hermaphroditism is presumed to be the result of the secretion of ovarian hormones.<sup>20, 26, 29, 38</sup> The breast enlargement should not be called gynecomastia, however, because the individual is not a male, but both a male and a female. The gynecomastia of pseudohermaphroditism is probably the result of hyperactivity of the adrenal cortex.<sup>26, 29, 38, 75</sup>

Pituitary disease (eosinophilic, basophilic and chromophobe adenoma) is frequently mentioned as a cause of gynecomastia, but the evidence for such an association is not well substantiated.<sup>12, 26, 29, 33, 38, 46, 49</sup>

After the elimination of adrenal disease, testicular disease, hepatic disease, starvation and malnutrition, congestive heart failure, Albright's disease, pseudohermaphroditism and pituitary disease, there is still a large number of disorders which have been reported to produce gynecomastia. These include bronchogenic carcinoma, chronic suppurative lung disease, transverse myelitis with paraplegia, chronic ulcerative colitis, diabetes mellitus, renal tumors, hyperthyroidism, leprosy, sarcoma of bone with pulmonary metastasis, and prostatectomy.<sup>4, 9, 10, 19, 20, 29, 31, 43, 46, 55, 65, 67</sup> The mechanism which results in gynecomastia in these disorders is obscure, but combinations of the explanations already discussed are employed by various authors to explain the gynecomastia.

*Data Derived from an Analysis of 160 Patients with Gynecomastia.* The records of all patients (a total of 160 cases) with gynecomastia who were seen at the University of Virginia Hospital and the University of Michigan Hospital between the years 1942 and 1952 were reviewed with special reference to the following:

1. Age of onset of the gynecomastia.
2. Duration of the gynecomastia.
3. Whether gynecomastia was unilateral or bilateral.
4. Presence or absence of systemic disease.
5. Duration of systemic disease.
6. Weight gain or loss.

7. Administration of digitalis.
8. Presence or absence of testicular, pulmonary, hepatic, renal or cardiovascular disease.
9. Laboratory findings, including hormone determinations (follicle stimulating hormone, 17-ketosteroid, Aschheim-Zondek test, estrogen).
10. Microscopic examination of breast and testicular tissue.

The 160 cases were divided, on the basis of age of onset of the gynecomastia, into two groups. In the patients of Group I the gynecomastia began before age 25; in those of Group II the gynecomastia appeared after age 25.

#### GROUP I

The following causes of gynecomastia were found in Group I (onset before the age of 25):

1. Gynecomastia of the newborn	1 Case
2. Gynecomastia in conjunction with puberty and adolescence	67 Cases
3. Gynecomastia in conjunction with stilbestrol given for alopecia areata	1 Case
4. Gynecomastia in conjunction with underlying disease:	4 Cases
(1) Carcinoma of the right testicle	1 Case
(2) Paraplegia from fracture of T <sub>11</sub>	1 Case
(3) Chronic glomerulonephritis	1 Case
(4) Eunuchoidism with bilateral cryptorchidism	1 Case
<b>Total</b>	<b>73 Cases</b>

1. *Gynecomastia of the Newborn*: Enlargement of the right breast was discovered at one month of age in one case. The gynecomastia was still present one month later. The physical examination was negative except for the breast changes, and routine chest x-rays and blood studies were normal. This case appeared to be an example of gynecomastia of the newborn in which resolution of the changes in the breast was delayed.

2. *Gynecomastia in Conjunction with Puberty and Adolescence*: Gynecomastia was listed as a manifestation of puberty or adolescence in 67 patients. The average age of onset was 15.5 years, the youngest patient being 11 years and the oldest 25 years at the time of onset. Gynecomastia affected the right breast in 22 instances, the left breast in 16 instances and both breasts in 29 instances. There was no evidence of systemic disease of any type in 48 of the 67 patients. Systemic diseases or congenital anomalies not etiologically related to the gynecomastia, insofar as could be determined, were present in 19 patients.

Weight changes were recorded in 11 patients: seven gained weight and four lost weight. No correlation was noticed between the onset of gynecomastia and a gain or loss of weight. Follicle stimulating hormone determinations were done on seven patients, 17-ketosteroid determinations on 11, estrogenic hormone determinations on six, and Aschheim-Zondek tests on eight. These tests all revealed values within normal limits. Liver function studies were performed on four patients, with normal results. No testicular biopsies were done. Biopsies of breast tissue were done in 19



patients, and varying amounts of mammary gland duct proliferation, connective tissue proliferation, increased vascularity, cellular infiltration and fat deposition were found.

Preexisting gynecomastia became more pronounced in two patients with the onset of a systemic disease. The onset of active pulmonary tuberculosis at the age of 24 was associated with further enlargement of the right breast of a patient who had initially noticed enlargement of this breast at age 12. Right gynecomastia had been present in a second patient since age 13. When he had right upper lobe pneumonia at age 22 the breast doubled in size.

3. *Gynecomastia in Conjunction with the Administration of Stilbestrol for Alopecia Areata:* At age 17 the patient was given an unknown amount of stilbestrol for the treatment of alopecia areata. Both breasts enlarged and remained enlarged for three and one-half years after the stilbestrol was discontinued.

4. *Gynecomastia in Conjunction with Underlying Disease:* Gynecomastia was probably etiologically related to an underlying disease in four patients:

Bilateral gynecomastia appeared at the age of 13 in one patient and was still present at age 27. Physical examination at age 27 revealed bilateral cryptorchidism, bilateral gynecomastia, eunuchoid bodily habitus, feminine hair distribution, small prostate and a small penis. Hormone studies were not done.

The second patient developed chronic glomerulonephritis at age 18 and gynecomastia appeared at age 23. Bilateral gynecomastia and chronic glomerulonephritis (hypertension, cylindruria, albuminuria; urea clearance, 40 per cent; nonprotein nitrogen, 55 mg. per cent) were found when the patient was examined at age 28. The cephalin flocculation and brom-sulfalein retention liver function tests were normal and the serum proteins were normal; 17-ketosteroid excretion was 15.9 mg./24 hours. The liver edge was palpable but the testicles and lungs were normal.

An accident at the age of 17 caused a fracture of the eleventh thoracic vertebra and paraplegia in the third patient. Urinary tract infection and kidney and bladder stones were troublesome during the eighteenth year, and the patient lost 40 pounds of weight. Bilateral gynecomastia was found at age 19. The testicles were found to be normal but the prostate was small on physical examination. Laboratory examinations indicated urinary tract infection, normal renal function, normal serum proteins and mild hypochromic anemia.

In the fourth patient, the right testicle was removed because of carcinoma at the age of 23, and right gynecomastia appeared at the age of 24. Except for the absence of the right testicle the physical examination was normal at age 24. The chest x-ray was normal and the Aschheim-Zondek test was negative. Microscopic examination of breast tissue showed findings compatible with a diagnosis of gynecomastia. The patient was not followed and it was therefore not possible to say whether metastases eventually developed.



## GROUP II

The following causes of gynecomastia were found in Group II (onset after the age of 25) :

1. Gynecomastia resulting from hormone administration	5 Cases
(1) Stilbestrol given for carcinoma of the prostate	4 Cases
(2) Male and female hormones given for psychoneurosis and prostatitis	1 Case
2. Gynecomastia in conjunction with an underlying disease	57 Cases
(1) Chorio-epithelioma of the testicle with metastases	1 Case
(2) Adenocarcinoma of the testicle	1 Case
(3) Unclassified testicular tumor	1 Case
(4) Seminoma of the testicle	1 Case
(5) Abscess of the testicle	1 Case
(6) Klinefelter's syndrome	2 Cases
(7) Hyperthyroidism	2 Cases
(8) Diabetes mellitus	3 Cases
(9) Cirrhosis of the liver	2 Cases
(10) Bronchogenic carcinoma	4 Cases
(11) Lung abscess	1 Case
(12) Bronchiectasis	2 Cases
(13) Empyema	1 Case
(14) Pulmonary tuberculosis	2 Cases
(15) Pneumonitis and atelectasis in course of anterior poliomyelitis	1 Case
(16) Appendicitis with prolonged convalescence	1 Case
(17) Rheumatoid arthritis	4 Cases
(18) Bilateral cryptorchidism and probable lymphoblastoma	1 Case
(19) Mycosis fungoides	1 Case
(20) Hypersplenic anemia, malnutrition, subdiaphragmatic abscess, and hemosiderosis of the liver secondary to multiple blood transfusions	1 Case
(21) Angiodermatomyositis	1 Case
(22) Unclassified collagen disease	1 Case
(23) Generalized nonspecific dermatitis	3 Cases
(24) Generalized psoriasis	1 Case
(25) Spinal cord injury with paraplegia	1 Case
(26) Fracture of L <sub>1</sub> , L <sub>2</sub> and tibia plus weight loss	1 Case
(27) Multiple vitamin deficiency and malnutrition	1 Case
(28) Chronic pyelonephritis	4 Cases
(29) Hypertension	9 Cases
(30) Arteriosclerotic heart disease and congestive failure	2 Cases
3. Gynecomastia which may have been related to the underlying disease.*	14 Cases
(1) Possible bronchiectasis	1 Case
(2) Pulmonary tuberculosis	1 Case
(3) Repeated syncope, cause unknown	1 Case
(4) Spontaneous pneumothorax	1 Case
(5) Substernal pain, cause unknown	1 Case
(6) Chronic maxillary sinusitis	1 Case
(7) Questionable hypothyroidism	1 Case
(8) Weight loss, gastrointestinal symptoms and questionable abdominal mass	1 Case
(9) Benign prostatism	1 Case
(10) Asthma, allergic rhinitis, colitis, sinusitis	1 Case
(11) Undescended left testicle	1 Case
(12) Questionable posterior mediastinal mass	1 Case
(13) Undiagnosed right upper quadrant pain	1 Case
(14) Syphilis of undetermined activity	1 Case
4. Gynecomastia with no demonstrable underlying disease	11 Cases
Total	87 Cases

\* The relationship between the underlying disease and gynecomastia was not clear or there was some doubt about the exact diagnosis of the underlying disorder.

1. *Gynecomastia Resulting from Hormone Administration:* Bilateral gynecomastia appeared during the course of stilbestrol administration for carcinoma of the prostate in four patients (ages 53, 53, 69 and 74). A fifth patient, who was given estrogen and androgen for treatment of psycho-neurosis and prostatitis, developed bilateral gynecomastia at the age of 38.

2. *Gynecomastia in Conjunction with an Underlying Disease:* An underlying disease appeared to be related to gynecomastia on etiologic grounds in 57 patients. Data on these patients are presented in table 1 (Gynecomastia Accompanying Systemic Disease in Patients Over Age 25).

3. *Gynecomastia Which May Have Been Related to the Underlying Disease:* The 14 cases in this group are not reviewed in detail because none of these patients was completely studied. In spite of insufficient data, it seems probable that there was an etiologic relationship between gynecomastia and systemic disease in many of these patients.

4. *Gynecomastia with No Demonstrable Underlying Disease:* There were 11 patients in this group. All of these patients were incompletely investigated as far as the cause of the gynecomastia was concerned.

In the 160 patients of Group I and Group II the right breast was involved in 43 patients, the left breast in 64 patients, and both breasts were involved in 53 patients. In the patients with bilateral gynecomastia, one breast frequently enlarged a few weeks or a few months before the other. All six patients whose gynecomastia was a result of hormone administration had bilateral gynecomastia. Bilateral gynecomastia had a tendency to occur in association with testicular tumors, cirrhosis of the liver, paraplegia from transverse myelitis, and chronic exfoliative dermatitis. The gynecomastia tended to be unilateral when it was found in association with hypertension, diabetes and rheumatoid arthritis. It was as often unilateral as bilateral when it occurred in conjunction with pulmonary disease, hyperthyroidism and puberty.

#### DISCUSSION OF ETIOLOGIC POSSIBILITIES SUGGESTED BY A STUDY OF THE 160 CASES

Analysis of the patients in whom gynecomastia developed as a result of puberty did not provide helpful information about the etiology of gynecomastia. The routine clinical hormone studies and liver function tests gave results within the normal range. A hormonal approach to the problem of pubertal gynecomastia has certainly not been exhausted in this study. The tests may not have been sensitive enough, they may not have been done frequently enough, they may have been performed at the wrong time (i.e., after the gynecomastia was well developed instead of during the phase of development when hormonal changes might be more easily measured), or hormones other than those tested for may have been involved.

Testicular disease produced gynecomastia by more than one mechanism in this series of cases. When gynecomastia was caused by testicular tumor,

TABLE I  
Gynecomastia Accompanying Systemic Disease in Patients Over Age 25

Age at Onset Sex	Systemic Disease	Weight Change	Liver Size	Testes Below	Blood Pressure	Chest X-ray	FBS	ERT	IT MS	A-2	Liver Function Tests	Urine
45	Choriocarcinoma II. Testicle removed age 40. Gynecomastia demonstrated 5 mos. later.	0	4 cm.	Left re- moved 10	110 110	Meta- stases					IGT, ind. 33 Ser. proc. 5.8	Urine normal
37	Gynecomastia presenting com- plaint. Mediastinal adenocar- cinoma demonstrated 4 mos. later. Regional metastases. 3 yrs. post-op no metastases and gynecomastia had dis- appeared.	Gain 15 lbs.	0	Right en- larged 10	114 100	Normal		6.8				CBC normal Urine normal
35	Right testicle removed age 13. Retroperitoneal and pulmonary metastases found age 35. Gynecomastia developed 5 mos. later.	Loss 20 lbs.	Palpable	Left removed	114 74	Meta- stases		0.8				CBC normal Urine normal
44	Left testicle removed 1 yr. before gynecomastia appeared. No metastases evi- dent 2 yrs. later.	0	0	Left re- moved 70	147 70	Normal						Asymia Urine normal
61	Left testicular atresia removed 1 yr. before gynecomastia developed.	0	0	Left re- moved 74	130 74	Normal						CBC normal Urine normal
31	Klinefelter's syndrome several years. Gynecomastia 4.5 yrs.	0	0	Both small	...	Normal			7.2			No sperm in ejaculate CBC normal Urine normal
23	Klinefelter's syndrome several years. Gynecomastia 5 mos. Hyperthyroid 2 mos. Treated with thioridol 1 mo. before gynecomastia appeared.	Gain 20 lbs. Loss 10 lbs.	0 0	Both in- fertile Normal	120 135 80	Normal	Neg. (7)	Normal	17.5		Cholest. 248 Cholest. 248 after treatment	CBC normal Urine normal BMR 150 before Rx. BMR 120 after Rx. Glycosuria Urine normal
43	Hyperthyroidism. Gyneco- mastia presenting complaint. 25 lbs.	Loss 25 lbs.	0	Normal	135 80	Normal		Normal	6.3			BMR 160 CBC normal Urine normal Glycosuria Urine normal
48	Diabetes with osteitis found 1 yr. after gynecomastia appeared. Alcoholism and hypertension unknown duration. Diabetes, metastatic carcinoma, gynecomastia, and osteitis re- sulted. Each time re- lapsed unknown.	Loss 20 lbs.	1 cm.	Right cryptor- chid	135 110 115 100	Normal					Diabetic G T T (ind.) Diabetic G T T	CBC normal Alb. normal Glycosuria
45	Diabetes mellitus discovered 4 mos. after gynecomastia appeared.	0	0	Normal	130 80	Normal						Diabetic G T T
49	Grimoni's 3 yrs. Aortic, esophageal varices. Pleural effusion. Edema. Gynecomastia appeared.	Loss 20 lbs.	10 cm.	Right cryptor- chid	105 35	Pleural effusion					Grossly abnormal	Leucocytosis Urine normal
38	Grimoni's 1 yr. Esophageal varices. Jaundice. Gyneco- mastia unknown duration.	Loss 20 lbs.	8 cm.	Normal	144 78	Normal					Grossly abnormal	Asymia Urine normal
71	Bronchogenic carcinoma diagnosed 4 mos. after gynecomastia appeared.	Loss 40 lbs.	0	Normal	105 60	Neoplasm						Long biopsy = carcinoma Asymia Urine normal
66	Compensated aortic aortic heart disease 24 mos. Gyneco- mastia 11 mos. Bronchogenic carcinoma diagnosed 11 mos. Clubbed fingers and toes.	Loss 12 lbs.	0	Normal	134 80	Neoplasm						Asymia Albuminuria Cells and cells in urine
41	Carcinoma right bronchus 1 yr. before gynecomastia. Clubbed fingers and toes. Living 3 yrs. after surgery.	Loss 20 lbs.	0	Normal	130 80	Neoplasm						Long biopsy = carcinoma Asymia Urine normal

TABLE I—Continued

47	47	L*	Bronchogenic carcinoma RUL, diagnosed two yrs. before gynecomaastia appeared.	Loss 15 lbs.	0	Normal	...	Scapular bag.	Normal	6, 4	Hgb. bilirubin, ser. prot., uric acid, creatin., flocc. normal. High rise of G T T not fall to normal at 3 hr. G T T and BSP normal.	Acemia Urine normal
49	49	B*	Long abscess 3 yrs. duration. Lost 15 lb. but had gained 25 lbs. and abscess cured when given protein and vitamin B <sub>12</sub> . Deficiency of protein and vitamin B <sub>12</sub> before gynecomaastia appeared. Chills frequent.	Gain 25 lbs.	0	Normal	102/65	Cervical Abscess	Normal	6, 3	Beg. wafers test negative	ChC normal Urine normal
73	73	R*	Long abscess 3 yrs. duration. Lost 15 lb. but had gained 25 lbs. and abscess cured when given protein and vitamin B <sub>12</sub> . Deficiency of protein and vitamin B <sub>12</sub> before gynecomaastia appeared. Chills frequent.	Loss 25 lbs. in 10 yrs.	0	Normal	102/65	Cervical Abscess	Normal	6, 3	Beg. wafers test negative	ChC normal Urine normal
47	47	L*	Long abscess 3 yrs. duration. Lost 15 lb. but had gained 25 lbs. and abscess cured when given protein and vitamin B <sub>12</sub> . Deficiency of protein and vitamin B <sub>12</sub> before gynecomaastia appeared. Chills frequent.	Loss 25 lbs. in 10 yrs.	0	Normal	102/65	Cervical Abscess	Normal	6, 3	Beg. wafers test negative	ChC normal Urine normal
36	36	B	Long abscess 3 yrs. duration. Lost 15 lb. but had gained 25 lbs. and abscess cured when given protein and vitamin B <sub>12</sub> . Deficiency of protein and vitamin B <sub>12</sub> before gynecomaastia appeared. Chills frequent.	Loss 25 lbs. in 10 yrs.	0	Normal	102/65	Cervical Abscess	Normal	6, 3	Beg. wafers test negative	ChC normal Urine normal
54	54	B*	Long abscess 3 yrs. duration. Lost 15 lb. but had gained 25 lbs. and abscess cured when given protein and vitamin B <sub>12</sub> . Deficiency of protein and vitamin B <sub>12</sub> before gynecomaastia appeared. Chills frequent.	Loss 25 lbs. in 10 yrs.	0	Normal	102/65	Cervical Abscess	Normal	6, 3	Beg. wafers test negative	ChC normal Urine normal
56	56	L*	Long abscess 3 yrs. duration. Lost 15 lb. but had gained 25 lbs. and abscess cured when given protein and vitamin B <sub>12</sub> . Deficiency of protein and vitamin B <sub>12</sub> before gynecomaastia appeared. Chills frequent.	Loss 25 lbs. in 10 yrs.	0	Normal	102/65	Cervical Abscess	Normal	6, 3	Beg. wafers test negative	ChC normal Urine normal
31	31	L*	Long abscess 3 yrs. duration. Lost 15 lb. but had gained 25 lbs. and abscess cured when given protein and vitamin B <sub>12</sub> . Deficiency of protein and vitamin B <sub>12</sub> before gynecomaastia appeared. Chills frequent.	Loss 25 lbs. in 10 yrs.	0	Normal	102/65	Cervical Abscess	Normal	6, 3	Beg. wafers test negative	ChC normal Urine normal
41	41	L	Long abscess 3 yrs. duration. Lost 15 lb. but had gained 25 lbs. and abscess cured when given protein and vitamin B <sub>12</sub> . Deficiency of protein and vitamin B <sub>12</sub> before gynecomaastia appeared. Chills frequent.	Loss 25 lbs. in 10 yrs.	0	Normal	102/65	Cervical Abscess	Normal	6, 3	Beg. wafers test negative	ChC normal Urine normal
75	75	L	Long abscess 3 yrs. duration. Lost 15 lb. but had gained 25 lbs. and abscess cured when given protein and vitamin B <sub>12</sub> . Deficiency of protein and vitamin B <sub>12</sub> before gynecomaastia appeared. Chills frequent.	Loss 25 lbs. in 10 yrs.	0	Normal	102/65	Cervical Abscess	Normal	6, 3	Beg. wafers test negative	ChC normal Urine normal
53	53	L*	Long abscess 3 yrs. duration. Lost 15 lb. but had gained 25 lbs. and abscess cured when given protein and vitamin B <sub>12</sub> . Deficiency of protein and vitamin B <sub>12</sub> before gynecomaastia appeared. Chills frequent.	Loss 25 lbs. in 10 yrs.	0	Normal	102/65	Cervical Abscess	Normal	6, 3	Beg. wafers test negative	ChC normal Urine normal
43	43	R*	Long abscess 3 yrs. duration. Lost 15 lb. but had gained 25 lbs. and abscess cured when given protein and vitamin B <sub>12</sub> . Deficiency of protein and vitamin B <sub>12</sub> before gynecomaastia appeared. Chills frequent.	Loss 25 lbs. in 10 yrs.	0	Normal	102/65	Cervical Abscess	Normal	6, 3	Beg. wafers test negative	ChC normal Urine normal
47	47	R	Long abscess 3 yrs. duration. Lost 15 lb. but had gained 25 lbs. and abscess cured when given protein and vitamin B <sub>12</sub> . Deficiency of protein and vitamin B <sub>12</sub> before gynecomaastia appeared. Chills frequent.	Loss 25 lbs. in 10 yrs.	0	Normal	102/65	Cervical Abscess	Normal	6, 3	Beg. wafers test negative	ChC normal Urine normal
65	65	L*	Long abscess 3 yrs. duration. Lost 15 lb. but had gained 25 lbs. and abscess cured when given protein and vitamin B <sub>12</sub> . Deficiency of protein and vitamin B <sub>12</sub> before gynecomaastia appeared. Chills frequent.	Loss 25 lbs. in 10 yrs.	0	Normal	102/65	Cervical Abscess	Normal	6, 3	Beg. wafers test negative	ChC normal Urine normal
61	61	B	Long abscess 3 yrs. duration. Lost 15 lb. but had gained 25 lbs. and abscess cured when given protein and vitamin B <sub>12</sub> . Deficiency of protein and vitamin B <sub>12</sub> before gynecomaastia appeared. Chills frequent.	Loss 25 lbs. in 10 yrs.	0	Normal	102/65	Cervical Abscess	Normal	6, 3	Beg. wafers test negative	ChC normal Urine normal

TABLE I—Continued

Age at Exam. Sex <sup>a</sup> Location	Gynecomastia Exam. Age of Onset	Systemic Diseases	Weight Change lbs.	Liver Exam. Palpable	Testicles Exam. Normal	Blood Pressure	Chart X-ray	FSH	EST	17 KB	A-2	Liver Function Tests	Other Laboratory Tests
61	41	M <sup>a</sup> Hypersplenism anemia 3 yrs., subdiaphragmatic masses after splenectomy, 1950, benign adenoma of liver 2 mos. before gynecomastia. Gaining weight at time of gynecomastia.	Loss & Gain	Palpable	Normal	104 90	Feuritis osteomyelitis	Pos.	Normal	8.8		Ser. prot. 8.5, alb. 4.5, glob. 17. Cholesterol 198	Renal function normal Acid biopsy abnormal Alkaline Albuminuria
41	41	B <sup>a</sup> Agglutination precipitin 2 yrs. after splenectomy, 1950, condition improved. Pleuritis and pneumonia during active phase of disease.	Loss 20 lbs.	Palpable	Biateral atrophy	104 90	Empty- sac Pneumonia	Pos.	Normal	8.8		Ser. prot. 8.5, alb. 4.5, glob. 17. Cholesterol 198	Renal function normal Acid biopsy abnormal Alkaline Albuminuria
55	55	B <sup>a</sup> Unclassified collagen disease with scleroderma, 1940, Cribbed bone x-ray, 1947. Fibrosis and amyotrophy.	Loss 20 lbs.	Palpable	Biateral atrophy	104 90	Empty- sac Pneumonia	Pos.	Normal	8.8		Ser. prot. 8.5, alb. 4.5, glob. 17. Cholesterol 198	Renal function normal Acid biopsy abnormal Alkaline Albuminuria
65	65	B <sup>a</sup> Gynecomastia developed 2 mos. after attack dermatitis with autoinflammation and autoinflammation. As dermatitis improved	0	Palpable	...	150 80	Normal	Pos.	Normal	8.8		Ser. prot. 8.5, alb. 4.5, glob. 17. Cholesterol 198	Renal function normal Acid biopsy abnormal Alkaline Albuminuria
64	64	B <sup>a</sup> Gynecomastia developed 3 mos. after contact dermatitis with autoinflammation and autoinflammation. As dermatitis improved	0	Palpable	...	150 80	Normal	Pos.	Normal	8.8		Ser. prot. 8.5, alb. 4.5, glob. 17. Cholesterol 198	Renal function normal Acid biopsy abnormal Alkaline Albuminuria
48	48	L <sup>a</sup> Life. Generalized dermatitis preceded left gynecomastia which appeared 2 mos. after attack. As dermatitis improved later, Right gynecomastia appeared 6 mos. after recurrence.	Loss 20 lbs.	Palpable	Biateral atrophy	104 90	Empty- sac Pneumonia	Pos.	Normal	8.8		Ser. prot. 8.5, alb. 4.5, glob. 17. Cholesterol 198	Renal function normal Acid biopsy abnormal Alkaline Albuminuria
80	80	B <sup>a</sup> Gynecomastia appeared 1 mos. after generalized psoriasis. Patient re- ceiving digitalis.	0	Palpable	Biateral atrophy	104 90	Empty- sac Pneumonia	Pos.	Normal	8.8		Ser. prot. 8.5, alb. 4.5, glob. 17. Cholesterol 198	Renal function normal Acid biopsy abnormal Alkaline Albuminuria
34	34	B <sup>a</sup> Biateral gynecomastia appeared 2 mos. after transverse myelitis.	0	Palpable	Biateral atrophy	104 90	Empty- sac Pneumonia	Pos.	Normal	8.8		Ser. prot. 8.5, alb. 4.5, glob. 17. Cholesterol 198	Renal function normal Acid biopsy abnormal Alkaline Albuminuria
53	53	L <sup>a</sup> Fracture T-12 and left tibia 4 mos. before gyneco- mastia. Lost 60 lbs period.	Loss 40 lbs.	Palpable	Biateral atrophy	104 90	Empty- sac Pneumonia	Pos.	Normal	8.8		Ser. prot. 8.5, alb. 4.5, glob. 17. Cholesterol 198	Renal function normal Acid biopsy abnormal Alkaline Albuminuria
78	78	B <sup>a</sup> Gynecomastia appeared 16 mos. after malnutrition, vitamin deficiency, weight loss, 1950, 1951, 1952. Mild hypernatremia.	Loss 20 lbs.	Palpable	Biateral atrophy	104 90	Empty- sac Pneumonia	Pos.	Normal	8.8		Ser. prot. 8.5, alb. 4.5, glob. 17. Cholesterol 198	Renal function normal Acid biopsy abnormal Alkaline Albuminuria
50	50	L <sup>a</sup> Symptoms of chronic pyelonephritis 4 yrs. before gynecomastia. Bi. congenital hypertension.	0	Palpable	Biateral atrophy	104 90	Empty- sac Pneumonia	Pos.	Normal	8.8		Ser. prot. 8.5, alb. 4.5, glob. 17. Cholesterol 198	Renal function normal Acid biopsy abnormal Alkaline Albuminuria
80	80	B <sup>a</sup> Biateral chronic pyelo- nephritis 8 mos. before gynecomastia. Grade III retinitis.	Loss 17 lbs.	Palpable	Biateral atrophy	104 90	Empty- sac Pneumonia	Pos.	Normal	8.8		Ser. prot. 8.5, alb. 4.5, glob. 17. Cholesterol 198	Renal function normal Acid biopsy abnormal Alkaline Albuminuria





primary or metastatic, it was bilateral, and the Aschheim-Zondek test was positive. Gynecomastia followed unilateral orchiectomy in three other patients (one testicular abscess and two testicular tumors). In two of these three patients the gynecomastia was unilateral, and in all three the Aschheim-Zondek test was negative. The testicular tubules showed varying degrees of atrophy in the five patients whose testicles were examined microscopically (metastatic chorio-epithelioma, Klinefelter's syndrome, hemosiderosis, generalized atopic dermatitis and mycosis fungoides). Did the tubular atrophy in these cases bear an etiologic relationship to the gynecomastia, was it a result of the same process that caused gynecomastia, or was it entirely unrelated? It appears, after analyzing these cases, that too much testicular tissue or too little testicular tissue, as well as qualitative changes in testicular tissue, is capable of producing gynecomastia.

Enlargement of the liver suggested hepatic dysfunction as a cause for gynecomastia in a number of conditions. Five of the nine patients with hypertension, both patients with arteriosclerotic heart disease, two of the four patients with pyelonephritis, and one of the four patients with generalized exfoliative skin disease had a palpable liver. Hepatic enlargement also occurred in rheumatoid arthritis (one case), diabetes mellitus (two cases), testicular tumor (two cases), angiodermatomyositis (one case), and bronchiectasis (one case). Routine liver function tests were abnormal in some of these patients and normal in others, but liver function tests were not done often enough to justify important conclusions.

The gynecomastia which occurred in conjunction with hypertension in nine patients, and with pyelonephritis in four others, was not caused by the administration of digitalis, because these patients had never been given this medicament. One patient with congestive heart failure was given digitalis six months after the gynecomastia developed, so digitalis could not have been an etiologic factor in the production of gynecomastia in this case. Digitalis could not be excluded from the list of possible causes of gynecomastia in another patient with congestive heart failure, inasmuch as he had been given digitoxin for one year before the gynecomastia appeared.

Altered adrenal function might be considered as an explanation for gynecomastia in patients with hypertension (essential hypertension, chronic pyelonephritis and glomerulonephritis), in view of the possible rôle of the adrenal cortex in the production of hypertension, and the known effect of adrenal hormones on breast tissue.<sup>23,47</sup> In fact, altered adrenal function should probably be considered as a possible mechanism in the production of gynecomastia in any serious disease. Urinary 17-ketosteroid values were low in 10 of 11 patients with gynecomastia and underlying disease in Group II (two cases of metastatic testicular tumor, one each of Klinefelter's syndrome, lung abscess, empyema, angiodermatomyositis, generalized atopic dermatitis, bronchogenic carcinoma, hyperthyroidism and mycosis fungoides). These values suggest adrenal hypofunction, but they do not take into account the possibility of imbalance of adrenal hormone production,

which might result in excessive or disproportionate elaboration of hormones which are potent agents in the production of gynecomastia.

It is well known that starvation and refeeding after starvation may cause gynecomastia in otherwise normal males. The same processes involved in starvation and refeeding may also be involved in the production of gynecomastia in some disease states, because many patients with chronic disease cannot eat normally and therefore lose weight, become anemic and develop hypoproteinemia. The gynecomastia may develop at the height of the disease (bronchogenic carcinoma, bronchiectasis, empyema, pulmonary tuberculosis, rheumatoid arthritis, collagen disease, generalized skin disease, multiple fractures, pyelonephritis, hyperthyroidism and diabetes), but it may also occur during convalescence when the patient is gaining weight, and the hemoglobin and serum proteins are reverting to normal. Gynecomastia appeared in this series during the recovery phase of appendicitis, hypersplenic anemia with subdiaphragmatic abscess and hemosiderosis, lung abscess, pulmonary tuberculosis and angiodermatomyositis.

#### CLINICAL IMPLICATIONS OF GYNECOMASTIA

Our data indicate that gynecomastia of the adult is frequently a manifestation of serious underlying disease (underlying disease present in 57 of 87 patients and probably present in several others). Gynecomastia may be the earliest sign of the disease, or it may receive major emphasis by the patient or physician while more subtle manifestations of disease go unnoticed. Gynecomastia between the ages of 11 and 25 is usually a part of the physiologic process of puberty and adolescence, but even during this age period enlargement of the breast may indicate some underlying disease (underlying disease present in four of 71 patients). Any case of gynecomastia therefore calls for a careful history, a careful physical examination and the necessary laboratory examinations. Particular attention should be directed to the testicles, the adrenal, the thyroid, the liver, the lung, the cardiovascular renal system and to the nutritional status of the patient.

It was anticipated, on the basis of previous reports, that gynecomastia might be found in association with a variety of diseases, including testicular tumors, Klinefelter's syndrome, hyperthyroidism, cirrhosis of the liver, bronchogenic carcinoma, suppurative lung disease, paraplegia from traumatic injury of the spinal cord, congestive heart failure, malnutrition and possibly diabetes. Gynecomastia was also expected to occur during puberty and after the administration of testicular, ovarian and adrenal hormones. It was a revelation, however, to encounter cases of gynecomastia in this series which apparently were the result of hypertension, chronic pyelonephritis, chronic glomerulonephritis, rheumatoid arthritis, chronic generalized skin disease, angiodermatomyositis and lymphoblastoma.

Many of the patients in this series had had breasts removed because the diagnosis of carcinoma of the male breast was entertained. Frequently too

much attention was given to the breast and too little to underlying conditions such as primary or metastatic testicular tumor, carcinoma of the lung, generalized skin disease, paraplegia, hyperthyroidism, diabetes, cardiovascular renal disease and puberty. Surgery is certainly indicated where there is real question of carcinoma of the breast, and it may be indicated because of tenderness or an undesirable cosmetic appearance, but there are probably many instances of unnecessary surgical removal of the male breast. This situation can be remedied by more careful examination of the breast, a better understanding of the causes of gynecomastia, and a more complete investigation of the patient before surgery is done.

#### CLINICAL CLASSIFICATION OF CONDITIONS ASSOCIATED WITH GYNECOMASTIA

A clinical classification of conditions associated with gynecomastia is suggested on the basis of information gleaned from the literature and from an analysis of the 160 cases reported herein.

##### I. Gynecomastia occurring as a result of a physiologic process:

1. Transitory gynecomastia of the newborn
2. Gynecomastia of puberty
3. Gynecomastia of hormone administration
  - a. Estrogens
  - b. Androgens
  - c. Chorionic gonadotrophin
  - d. Desoxycorticosterone acetate and other adrenal hormones

##### II. Gynecomastia occurring as a result of a pathologic process:

1. Testicular disease
  - a. Malignant tumors
    1. Hormone secreting
    2. Nonsecreting
  - b. Benign tumors
  - c. Atrophies
  - d. Inflammations
  - e. Castration and surgical removal of testicular tissue
  - f. Cryptorchidism
  - g. Klinefelter's syndrome
2. Pulmonary disease
  - a. Bronchogenic carcinoma
  - b. Bronchiectasis
  - c. Pulmonary tuberculosis
  - d. Empyema
  - e. Pneumonia

3. Cardiovascular disease
  - a. Hypertension
  - b. Congestive heart failure
4. Renal disease
  - a. Chronic pyelonephritis
  - b. Chronic glomerulonephritis
  - c. Renal neoplasm
5. Hepatic disease
  - a. Cirrhosis
  - b. Hepatitis
  - c. Carcinoma
6. Thyroid disease
  - a. Hyperthyroidism, untreated
  - b. Hyperthyroidism treated with  $I^{131}$  and propylthiouracil
7. Nervous system disease
  - a. Transverse myelitis with paraplegia
  - b. Other diseases of the spinal cord
8. Skin disease
  - a. Generalized exfoliative dermatitis
  - b. Generalized psoriasis
9. Pancreatic disease
  - a. Diabetes mellitus
10. Adrenal disease
  - a. Malignant tumor
  - b. Hyperplasia
  - c. Benign tumor
11. Pituitary disease
  - a. Acromegaly
  - b. Basophilic adenoma
  - c. Chromophobe adenoma
12. Hermaphroditism
  - a. True
  - b. Pseudo
13. Pineal gland disease
  - a. Tumor
14. Gastrointestinal tract disease
  - a. Chronic ulcerative colitis
  - b. Appendicitis with prolonged convalescence

15. Bone disease
  - a. Chronic osteomyelitis
  - b. Sarcoma with pulmonary metastasis
  - c. Multiple fractures
16. Collagen disease
  - a. Rheumatoid arthritis
  - b. Angiodermatomyositis
17. Lymphoblastoma
  - a. Mycosis fungoides
  - b. Others (?)
18. Malnutrition
  - a. Starvation
  - b. Protein deficiency
  - c. Vitamin B deficiency
19. Albright's disease
20. Prostatectomy

#### SUMMARY

1. A brief review of the theories concerning the etiology of gynecomastia has been presented.

2. Data derived from 160 cases of gynecomastia have been analyzed.

3. A previously unrecognized or unstressed relationship was found between gynecomastia and the following conditions: chronic generalized dermatitis, rheumatoid arthritis, angiodermatomyositis, lymphoblastoma, diabetes mellitus, chronic pyelonephritis, chronic glomerulonephritis and essential hypertension.

4. Gynecomastia beginning before age 25 was usually a manifestation of puberty.

5. Gynecomastia beginning after age 25 was usually a manifestation of a serious underlying disease.

6. Gynecomastia was occasionally the initial manifestation or the presenting complaint of a serious underlying disease.

7. A clinical classification of conditions associated with gynecomastia has been proposed.

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## CASE REPORTS

### A CASE OF EPIDEMIC HEMORRHAGIC FEVER IN THE UNITED STATES \*

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EPIDEMIC hemorrhagic fever presents a difficult diagnostic problem to physicians in the United States because of the bizarre leukemoid blood picture, the thrombocytopenia with petechiae followed by a rather typical lower nephron nephrosis syndrome. We present herewith a case which occurred in a civilian who was discharged from the Armed Forces November 21, 1953 at Camp Carson, Colorado, and who arrived in Kansas City, Missouri on November 22. He developed prodromal symptoms which consisted of fleeting dizzy sensations and fatigue on November 26 and 27 and became acutely ill on the evening of November 29.

#### CASE REPORT

J. F. H., male, age 26, left Kumwha, Korea, November 7, 1953 traveling airborne to Inchon, Japan, Honolulu, San Francisco, Denver, Colorado Springs, and Camp Carson, Colorado, arriving there November 20, 1953.

When seen by one of us at his home on November 30, he presented a picture of an acutely ill patient with a temperature of 104° F., mild pharyngitis, with excessive perspiration. He was given Duracillin under the impression that the pharyngitis, of a dry granular type, was the sole cause of his illness. Following this his blood count revealed 5,450 leukocytes and malaria smears were negative. His temperature ranged from 102° to 104° even though he was given 15 grains of aspirin every two hours until December 1. On that date, he complained of photophobia and his conjunctivae were suffused. He was admitted to St. Luke's Hospital that evening.

The only significant previous illnesses had been rheumatic fever as a child and infectious mononucleosis while in college, before entering service.

His chief complaints were severe headache, generalized aches and pains, and extreme weakness. On the following morning, he presented the picture of an acutely ill young male, perspiring profusely, with intermittent clouded sensorium. Our impression at this time, with a leukocyte count of 55,750, a platelet count of 28,000, a nonprotein nitrogen of 62 mg. per cent, and a 4 plus albuminuria, was Weil's disease, possibly a leukemoid reaction or an acute leukemia. At this time the differential revealed 4 myeloblasts, 3 promyelocytes, 8 myelocytes, 30 metamyelocytes, 42 polymorphonuclears, 3 eosinophils, 9 lymphocytes, and 1 monocyte with 7 nucleated red cells per 100 white blood cells. His hemoglobin was 98 per cent, with 5,500,000 red blood cells, which would be unusual for an acute leukemia. He was given penicillin, streptomycin, and one dose of Aureomycin intravenously with 2 liters of parenteral fluids. Sternal aspiration revealed a fairly normal bone marrow. His white count had risen to 93,500 on December 3 with a platelet count of 12,000. At this time numerous Downey cells were seen on the smears and his monocyte count

\* Received for publication January 18, 1954.



FIG. 1. Papanicolaou smear of urine sediment. The large mononuclear phagocyte in the center has a compressed, eccentric nucleus, a single large central cytoplasmic vacuole, and multiple small peripheral cytoplasmic vacuoles. A transitional epithelial cell is seen at the upper right. (Oil immersion).

reached 21 per cent on December 4 making us think of an atypical infectious mononucleosis. His temperature progressively returned toward normal and has remained normal since December 5.

On December 3 he complained of severe pains in the muscles and tendons around his knees. At this time his symptoms included anorexia and polydipsia. He stated that he passed small amounts of black tarry stools and vomited coffee grounds material on that date. Petechiae appeared on his conjunctivae and buccal mucosa the morning

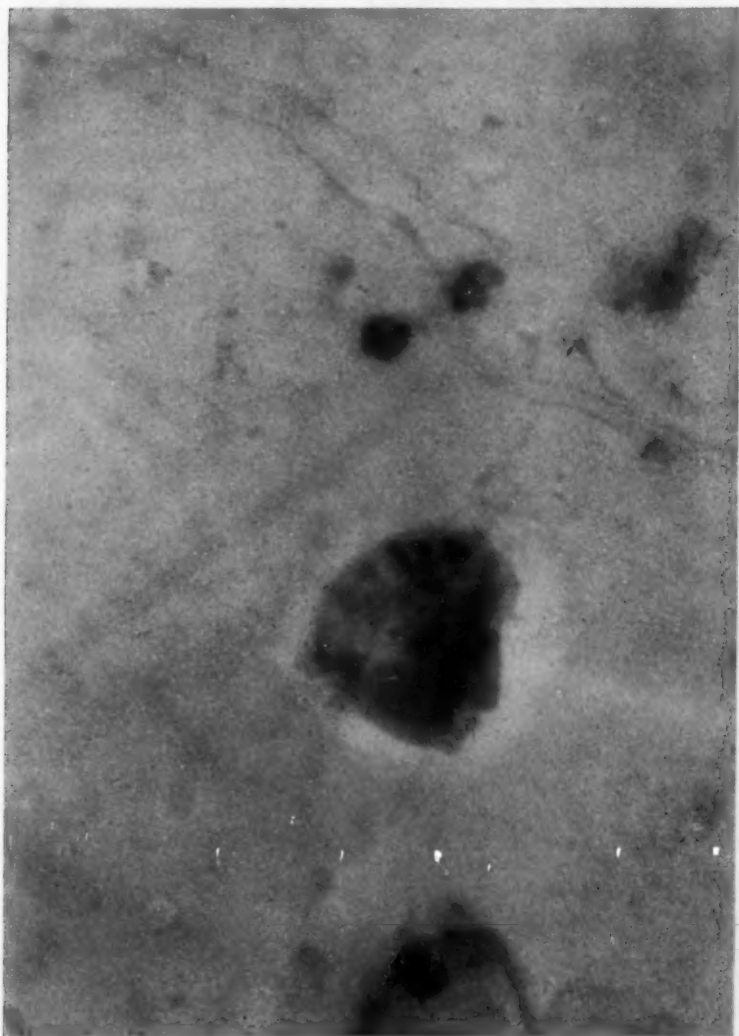


FIG. 2. Papanicolaou smear of urine sediment. A single phagocyte is seen that contains considerable nuclear debris and several degenerating red blood cells in the cytoplasm. Two lymphocytes are seen at the left. (High power field)

of December 4. It was not until the evening of December 4 that we realized we were dealing with a case of epidemic hemorrhagic fever. During this first week he was quite groggy, slept much of the time and was hard to arouse. At times it appeared difficult for him to concentrate.

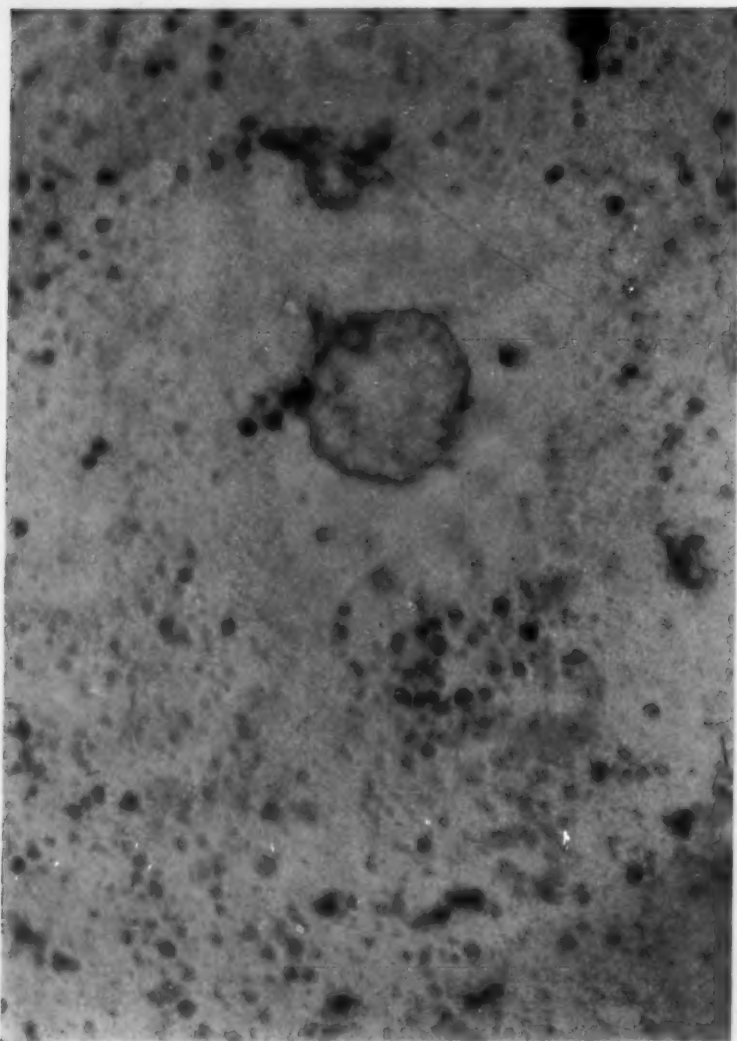


FIG. 3. Oil red O stain of urine sediment, showing many small dark fat droplets, and an irregularly outlined phagocyte, just to the left, center, that contains no fat. (Low power field)



TABLE I

	11-30	12-2	12-3	12-4	12-5	12-6	12-7	12-8	12-9	12-10	12-11	12-12	12-14	12-16	12-18	12-28	1-4
Mg. % NPN																	
Urinary albumin		62	72		110		137	120	110	110	110	110	91	78	64		36
Urine s.g. 1.0		4+		4+	Neg.	08	04	03	Neg.	04	03	04		12			
PSP 1 hr.		38		04				8%	08								
Creatine clearance									35.18 cc. per min. per 70K.						35% 48.87 cc. per min. per 70K.		48% 87.16 cc. per min. per 70K.
Fluid intake		3710	3060	2040	1100	2000	2950	3440	3580	4420	4470	4550	4280	5310	5890		
Fluid output		1480	2200	945	2850	3050	3760	3900	4435	4980	5275	6100	6270	6415	6350		
Wt.							153	151	150	147	146	145	141	143	141		

TABLE II

	11-30	12-2	12-3	12-4	12-5	12-6	12-7	12-8	12-9	12-10	12-11	12-12	12-14	12-16	12-18
WBC	5450	55,750	93,500	91,000	46,000	42,900	17,400	13,100	12,400	9200	9950	7400	7750	6600	10,800
Platelet $\times 1000$	28	28		12			16	36	70	102	120	110	72	124	180
Hb%	98	98	96	82	70	74	72		76	76	74	76		78	78
Myeloblasts	4														
Promyelocytes	3			6	2			7						2	Baso-
Myelocytes	8			16	13			20						1	phils 6
Metamyelocytes	30			49	52		62	44						70	54
Polys	3			2	2		2							5	1
Eosinophils	3			3	2									20	36
Lymphocytes	9			8	10		30	13						2	
Monocytes	1			21	21		6	13							
Nucleated red per 100 WBC	7			6				1							
Downey cells		numerous	numerous		numerous										3'
Bleeding time	3'4"				over 18'	10'									2'
Coagul. time	5'								9'						

As soon as we realized we might be dealing with a case of epidemic hemorrhagic fever we searched the urine for the mononuclear phagocytes that have been described by some observers as being characteristic of the disease. Large numbers were found (figure 1). They measured 20 to 45 microns and had the characteristic appearance of large phagocytic cells; at times they were mononuclear and at other times multinucleated, with foamy cytoplasm and cytoplasmic vacuoles. Some contained ingested erythrocytes (figure 2). Fat stains were negative (figure 3).

He improved clinically on December 5, when he became more alert and the profuse perspiration stopped. All chemotherapy was stopped on this date. His urinary output started to increase and continued to do so for the ensuing week, reaching levels of 6 liters a day.

His treatment was purely symptomatic with temporary limiting of fluid intake while his urinary output was decreased.

He developed buccal thrush on December 8 which promptly responded to gentian violet therapy, and which may have been related to the previous antibiotic therapy.

Heterophil antibodies were normal on two occasions in the hospital laboratory while the report on this patient, submitted by the Public Health Laboratory, Virus and Rickettsia Section, Montgomery, Alabama, showed no serologic evidence by complement fixation test of lymphocytic choriomeningitis, mumps, Eastern equine encephalomyelitis, Western equine encephalomyelitis, St. Louis encephalitis, epidemic typhus, murine typhus, rickettsial pox, Rocky Mountain spotted fever, influenza A, influenza B, Q fever, psittacosis and lymphogranuloma venereum group.

Our patient has had a satisfactory convalescence with a falling nonprotein nitrogen and an improving renal function as evidenced by phenolsulfonphthalein and creatine clearance tests. From previous reports, we anticipate complete recovery in this patient.

Tables 1 and 2 summarize the laboratory data.

#### SUMMARY

A typical case of epidemic hemorrhagic fever has been presented occurring in the United States in a civilian. This patient was a Korean veteran, who had left the endemic area at least three weeks previously. Excellent discussion of clinical and laboratory findings on this disease has been presented previously.<sup>1, 2, 3, 4, 5, 6</sup> It is possible that other cases may occur in the United States in individuals who have returned from Korea and its diagnosis presents a problem to the physician unfamiliar with the bizarre leukemoid blood picture, the petechiae and thrombocytopenia followed by a lower nephron nephrosis syndrome. The demonstration in the urine of the phagocytic cells said by some to be characteristic may help make an earlier diagnosis in other cases.

We are indebted to the personnel in the laboratory at St. Luke's Hospital for their interest and assistance in this case.

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## SEVERE REACTIONS TO PARA-AMINOSALICYLIC ACID: A CASE REPORT AND BRIEF REVIEW OF LITERATURE\*

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THE purpose of this paper is to report a severe reaction to para-aminosalicylic acid (PAS) and to present a brief review of the literature concerning PAS reactions. Since the introduction of PAS as an antituberculous agent in 1946 by Lehman, based on the work of Bernheim, there has been a worldwide use of the drug in the treatment of tuberculosis. The efficacy of PAS was confirmed by Sievers and Youmans and in 1949 Block et al. suggested that PAS in combination with streptomycin would aid in preventing development of drug resistance. Since then PAS has become accepted as a part of the preferred treatment of tuberculosis in combination with streptomycin or isoniazid.

Early reports in 1949 indicated that gastrointestinal upsets and occasional rash produced by 5 to 30 gm. per day of PAS were quite commonly encountered. Case reports in that year consisted of one case in which PAS crystals were found in the urine following hematuria and albuminuria. Four case reports from the Mayo Clinic<sup>1</sup> revealed that PAS caused fever, dermatitis, and one case of bullous eruption of the glans penis. All patients reacted later to a test dose of PAS, but none reacted to patch or skin testing. Reactions occurred from eight to 45 days after the onset of therapy. None reacted to a test dose of PABA but several had mild reactions to sodium salicylate.

In 1950 there were reports of urticaria and systemic reactions after five to 40 days of PAS therapy. Rash, fever, nausea, anorexia, emesis and diarrhea were well established complications of PAS use. It was also noted that patients could be desensitized to febrile and dermatologic reactions. Case reports of the more severe reactions emphasized the fever, rash and anorexia as common indications of PAS intolerance or impending reaction. The ability to reproduce the reactions with test doses was also well reported.<sup>2</sup> Several cases are reported with systemic reactions plus jaundice of minimal degree and eosinophilia of 30 per cent.<sup>3</sup> One case was reported of hypokalemia thought to be due to PAS, but a later review of 10 patients showed that sodium and potassium levels did not seem to be altered by PAS ingestion. A complete review of PAS toxicity by Lyght et al.<sup>4</sup> brought out the above-mentioned symptoms and signs, plus the fact that blood dyscrasias and changes in clotting mechanisms had not been encountered. Mild renal and ocular upsets seem to be transient and not a contraindication to PAS therapy.

In the next year a number of case reports again included fever, rash and anorexia. In addition, several unusual types were reported that have not been observed since. A case<sup>5</sup> simulating tuberculous meningitis with fever, stiff neck

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and elevated cells in the spinal fluid was observed after eight days on PAS therapy. Another case of myxedema in an eight and a half year old girl receiving PAS for 12 months is reported on the basis of clinical diagnosis. She returned to a normal state following cessation of the drug. Toxic hepatitis after four weeks of PAS therapy is cited, and the authors also mention five other known cases. Case reports and review of cases in the Swiss literature<sup>6</sup> mention a case of toxicity with albuminuria, leukocytosis and elevated prothrombin time. Another case manifested water retention, loss of potassium and hemolytic anemia. It was stated that severe PAS reactions may take the form of angioneurotic edema, anuria, polyneuritis, eosinophilia and perifocal pulmonary infiltrates. Reactions had a latent period after starting PAS of eight days to 10 weeks, and all disappeared rapidly following cessation of the drug. Reactions could usually be repeated by test doses of the drug, and desensitization was usually successful. A single case of hemolysis is reported after five days of PAS therapy, and another severe reaction occurred associated with petechial rash, icteric index of 35 units and an 18 per cent eosinophilia.

The more recent literature of 1952 and 1953 shows an excellent review by Warring and Howlett,<sup>7</sup> who found significant reactions in 2.5 per cent of 275 patients on PAS treatment. Fever and urticarial rash were the common manifestations, although they observed one unusual reaction in the form of an acute transitory pneumonitis with eosinophilia (Löffler's syndrome). Reports from the combined VA-Army-Navy Therapy Conference<sup>8,9</sup> reveal a 2.2 per cent incidence of reactions in 1,734 patients treated with PAS. Ninety-five per cent occurred in the first 16 weeks of therapy, and reactions were severe enough to warrant stopping the drug. Reactions seem to be independent of the type of PAS used. A case is reported with lymphadenopathy and sore throat in addition to fever, rash and anorexia. Another reaction was associated with elevated cerebrospinal fluid protein. Two cases of exfoliative dermatitis are reported, one of which later reacted to acetyl salicylic acid (ASA). The foreign literature produced several interesting case reports, one of a serum-sickness type of reaction which occurred during streptomycin and PAS therapy, in which patch tests were positive to both drugs. Another severe reaction with jaundice and tender liver showed a positive patch test to PAS which disappeared after successful desensitization.<sup>10</sup> A single case illustrating a severe reaction to PAS is reported here.

#### CASE REPORT

A 28 year old white male diabetic was admitted to the hospital because of uncontrolled diabetes and pulmonary tuberculosis. The diabetes mellitus had been known since 1945, and two months prior to admission a lung lesion was noted on Mobile Unit chest x-ray. The sputums were positive for acid-fast bacilli prior to admission. The patient had not received streptomycin, PAS or isoniazid previously. There was no history of allergy and no known drug or food intolerance. The family history of allergy was negative. Physical examination revealed a blood pressure of 100/60 mm. of Hg in a young male of healthy appearance. Moist râles were heard over the right apex posteriorly, and there was slightly increased transmission of spoken voice sounds in the same area. Initial laboratory studies revealed hemoglobin, 13.5 gm.; red blood cells, 4.68 millions; white blood cells, 6,200, with a normal differential count. The sedimentation rate was 11 mm. (Wintrobe method), urinalysis was normal except for a 4 plus sugar; serology was negative. Fasting blood sugar was 346 mg. per 100 ml.; nonprotein nitrogen, 26 mg./100 ml.; creatinine level, normal. A urine

concentration test showed concentration to 1.032, and the phenolsulfonphthalein excretion was normal. Sputums were positive on smear for acid-fast bacilli and subsequently positive to culture. A Hanger's test was negative and a second strength PPD skin test was positive.

*Course in Hospital:* The diabetes was well controlled with NPH insulin, 90 units daily, and an American Diabetes Association diet No. 4. The patient was started on 1 gm. of streptomycin (SM) twice weekly and PAS, gm. 16 daily. The patient's course was satisfactory, and after one month of hospitalization and several weeks of therapy he was transferred to this hospital. Therapy was continued as above except that PAS was reduced to 12 gm. per day. After two weeks on the antituberculous drugs the patient developed a dry scaly erythematous rash over both shoulders extending into the axillae which resembled tinea versicolor. On the twenty-eighth day after onset of therapy he complained of severe pruritus of the entire body, and the rash over

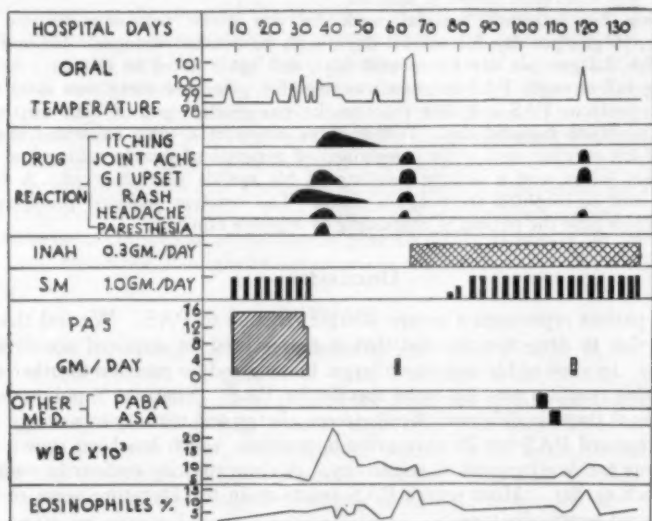


FIG. 1. Graphic picture of hospital course.

the upper thorax became more erythematous and macular in appearance. He complained of headache and a "pins-and-needles" feeling of his skin over the arms and legs. Later that day he noted muscle aching, joint pains and upset stomach, in addition to chills and fever. All medication was stopped and the symptoms gradually subsided over the next 17 days, during which time oatmeal baths and antihistamine drugs afforded some relief. At the height of reaction, his white blood cell count reached 24,000, with 12 per cent neutrophils, 68 per cent large lymphocytes, 11 per cent small lymphocytes and 8 per cent eosinophils. Minimal adenopathy was noted in the cervical, epitrochlear, axillary and inguinal lymph node regions. Liver and spleen were not enlarged or tender. It was felt that this was a drug reaction, and no further medication was given until the patient was asymptomatic. The rash and pruritus persisted for almost three weeks, and the eosinophil count remained at 8 to 9 per cent.

On the sixty-third hospital day a test dose of 4 gm. PAS was given. Several hours later the patient complained of nausea, fever and chills, and was noted to have

a mild urticaria. The day following he complained of sore throat and some tender cervical adenopathy. This reaction subsided promptly, and the blood count showed more eosinophilia and less leukocytosis than at the time of the primary reaction. The patient was started on isoniazid therapy without difficulty, and streptomycin was cautiously started. A skin test using 10 mg. of streptomycin gave no reaction, and the patient resumed streptomycin, 1 gm. twice a week, without difficulty. These two reactions seemed to have no untoward effect on the control of his diabetes other than his having to miss a few meals because of nausea and emesis. Laboratory work during the course of the two reactions revealed a normal urinalysis and negative heterophil antibody on two occasions; a repeat Hanger's test was also negative. The electrocardiograph was reported as normal, and progress chest x-rays remained stable. The patient tolerated streptomycin plus iso-nicotinic acid hydrazide (INAH) very well and continued to improve clinically, gaining 11 pounds during this period. He remained well controlled on NPH insulin.

During his sixteenth hospital week he was given para-aminobenzoic acid (PABA), 10 gm. per day for several days, with no unusual changes. He was then given ASA, 1.2 gm. per day for several days, and again noted no change. A patch test using full strength PAS solution was negative. Because there was some doubt about the previous PAS test dose reaction, he was given 4 gm. of PAS on the one hundred twentieth hospital day. Within three hours he became nauseated and had emesis of his evening meal. He complained of generalized muscle aching and stiffness of his joints, and a definite swelling of his eyelids was observed. A febrile response and eosinophilia were again noted. The reaction subsided promptly and at the present time the patient is continuing to improve clinically.

#### DISCUSSION

This patient represents a severe allergic reaction to PAS. We feel that this was not due to drug toxicity but that it represented an acquired sensitivity to the drug. In view of his negative allergic history and no reaction to other medications, this reaction was felt to be specific for PAS. Sherman<sup>11</sup> points out the difficulties at times in differentiation between allergy and toxicity to a drug. This patient received PAS for 28 days prior to reaction, which has been shown to be ample time for development of sensitivity. A drug toxicity ordinarily manifests itself much earlier. Most severe PAS reactions in the literature seem to be of the acquired sensitivity type.

#### SUMMARY OF CASE REPORTS

Major Systemic Reactions to PAS using 10-16 gm. per day

*Drug reaction after onset of therapy (21 cases)*

Range 6-45 days. Average, 20.6 days.

##### Patch Test

Positive—3  
Negative—7

##### Reactions to Test Dose

Positive—17  
Negative—none reported

##### Reactions to PABA

Positive—none reported  
Negative—6

##### Reactions to Salicylates

Positive—3  
Negative—4

##### Successful Desensitisation

Successful—7  
Failure—2



The summary of case reports shows that reactions to PAS may occur anywhere from six to 45 days after onset of therapy, and that the average is about three weeks. Patch tests are usually of no help, as noted in our case. Schwartz and Moyer<sup>8</sup> postulated cross sensitivity with PABA or salicylates due to the similarity to the chemical structure of PAS. No reactions to PABA are reported in PAS-sensitive patients. The cross sensitivity to salicylates may develop, three cases having been reported. It is probably wise to check cross sensitivity with salicylates in patients developing PAS reactions for future use of the physician and the patient. As is shown, 17 cases have been reported using test doses to confirm PAS sensitivity. It was true in this case that a test dose of PAS caused a reaction similar to the primary allergic reaction. No negative responses are reported to test doses; therefore, it is probably the most reliable method of proving the cause of the reaction. A test dose of 4 gm. of PAS was used in our case. Desensitization is usually successful, with only two failures reported. Steel<sup>10</sup> and Warring<sup>7</sup> have reported successful desensitization schedules. Steel recommended using 50 mg. per day in divided doses and increasing 50 mg. per day until the therapeutic dose of PAS is reached. Warring and Howlett gave from 0.01 gm. PAS up to 0.2 gm., and increased gradually in divided doses until full doses were reached. Their patients took from 15 to 54 days to become desensitized. The speed of desensitization depended on the day-by-day reactions of the patient. Our patient was not desensitized, as his medication at present consists of streptomycin plus INAH. However, in the advent of any drug resistance, it might be necessary in the future.

#### SUMMARY

Due to the increasing use of para-aminosalicylic acid (PAS) in the chemotherapy of tuberculosis, recognition of PAS reactions is important. Unusual types of reactions are cited, but in general the reactions fit into an acquired sensitivity pattern which is usually specific to PAS. The response is a general systemic reaction with fever, rash, nausea, emesis, joint aches, muscle pain, headache and sometimes mild paresthesias. Leukocytosis and eosinophilia are frequently seen. Reactions subside promptly when PAS is stopped, and a milder reaction with an eosinophilia can be obtained by using a test dose of the drug. Patients usually can be desensitized if it is desirable to continue PAS therapy. History of allergy or other types of drug intolerance does not necessarily indicate that PAS-acquired sensitivity will develop. In patients developing sensitivity to the drug, the reaction may be expected within the first six to seven weeks of therapy, the average being three weeks. Cross sensitivity to salicylates should be checked in sensitive patients. Patch testing is not reliable, and a test dose of the drug given orally seems to be the most definite means of implicating PAS as the drug at fault when sensitivity is suspected. A case is reported here which bears out these various generalizations on PAS reactions.

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## ACQUIRED SENSITIVITY TO HUMAN ALBUMIN FOLLOWING ALBUMIN TREATMENT OF IDIOPATHIC HYPOPROTEINEMIA \*

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SINCE concentrated human serum albumin has become available, it has been used extensively as ideal for parenteral protein replacement, and as a plasma volume expander.<sup>1</sup> It is estimated<sup>2</sup> that to date, 2,300,000 units of 25 gm. each have been prepared in the United States according to the method of Cohn and his associates.<sup>3</sup> Although "anaphylactoid,"<sup>4</sup> pyrogenic and hemodynamic<sup>5</sup> reactions have been noted to follow intravenous injections of human serum albumin, none due to natural or acquired sensitivity has been reported. Hence the development of sensitivity after repeated administration of albumin, with the appearance of precipitins in the serum of a patient with idiopathic hypoproteinemia, and successful treatment of the sensitivity by desensitization, seems worthy of report.

### CASE REPORT

A 44 year old married woman was admitted to the Peter Bent Brigham Hospital for the eleventh time on October 6, 1951. She had first noted dependent edema, fatigue and loss of ambition in 1938. Chronic diarrhea had been present from 1938 to 1940. Studies at a number of hospitals during the period 1940-1945<sup>6</sup> showed a persistently low total plasma protein level of the order of 4 gm. per cent, with an albumin-globulin ratio of 2:1 (Howe fractionation method). An electrophoretic study had shown the plasma protein to contain 48 per cent albumin, 10 per cent alpha-one globulins, 11 per cent alpha-two globulins, 19 per cent beta globulins, 7 per cent fibrinogen and 5 per cent gamma globulin. There was no clinical or laboratory evidence of liver disease, nephrosis or osteoporosis. Transfusions of plasma and whole blood raised the plasma protein level and gave temporary relief from the peripheral edema. During the period 1940-1945 the patient received approximately 100 infusions of whole blood or plasma.

The patient was admitted for the first time to the Peter Bent Brigham Hospital in May, 1945. The significant physical findings were bilateral ankle and pretibial edema, facial puffiness, a smooth, nontender liver edge two fingerbreadths below the right costal margin, and a blood pressure of 90/60 mm. of Hg. The laboratory data included a total protein of 4.5 gm. per cent, with an albumin concentration of 2.5 gm. per cent, a normal plasma amino acid level, a total cholesterol of 320 mg. per cent, with free cholesterol of 100 mg. per cent, and a nonprotein nitrogen of 27 mg. per cent. There was no evidence of hepatic involvement, of the nephrotic syndrome or of demineralization of bone. No significant proteinuria was found at that time or subsequently, although care was taken to measure the urinary protein during and after albumin infusions. Intravenous salt-poor concentrated human albumin was given for 10 days, with a subsequent elevation of the plasma protein to 6.5 gm. per cent. The facial and dependent edema subsided. Although the patient had no previous history

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of allergy, during this admission her record states that after an injection of Pituitrin the patient suffered an attack of "marked wide spreading urticaria lasting two hours," which was "poorly and slowly relieved by ephedrine." Following discharge from the hospital she continued to receive plasma and albumin infusions, the plasma administrations being curtailed after a severe case of homologous serum hepatitis was contracted three months following a plasma infusion. She appeared to recover completely from this illness, and showed no residual liver impairment.

From May, 1945, to September 1948, in the course of nine subsequent admissions to the Peter Bent Brigham Hospital, the patient was studied extensively, and no significant findings were made other than a persistent low serum albumin level, and an elevation of serum globulin and cholesterol. The hypoproteinemia and edema were refractory to treatment with oral protein hydrolysates, oral amino acids, liver extract, hydrochloric acid, Ventriculin, *L. casei* factor, low caloric and low salt diet, mercurial diuretics, and urea and ammonium chloride. The only therapy which could be relied on to give relief was human plasma protein, and from May, 1945, to September, 1948, the patient received approximately 4,750 gm. of concentrated, salt-poor albumin administered at irregular intervals. In November, 1947, her first reaction to an albumin infusion occurred. This is said to have consisted of pyrexia, a chill, and swelling, redness and urticaria of the left palm. During 1948 she began to have reactions with increasing frequency and severity. These attacks were reported as comprising chills, fever to 107° F., sweating and generalized hives. They occurred during a period from shortly after the onset of the infusion up to several hours after its completion. The reactions often lasted several days unless alleviated by the administration of antihistaminics.

Following the tenth admission, in September, 1948, the patient was not seen again until October, 1951. During this interval she continued to have severe reactions to albumin, therapy became progressively more difficult, and albumin was given only at prolonged intervals. It was also noted that hives broke out on the extremities during periods of emotional stress. ACTH in courses of 5 mg. every six hours for three days, and 10 mg. every six hours for seven days, as well as a course of cortisone therapy, did not improve the edema or abolish the urticaria following infusions of albumin. In the spring of 1950 a change of albumin was made from one commercial preparation to another, with a slight temporary decrease in the severity of the reactions. In 1951, "immunization," undertaken at another clinic, with 1 c.c. intravenous doses of albumin, was unsuccessful in abolishing the reactions, as was a small dose of cortisone, i.e., 12.5 mg. per day (given orally). A dose of 150 mg. of cortisone given orally and followed by 20 c.c. of albumin intravenously did not prevent chills and fever, which lasted for three days. Because of these reactions albumin therapy was abandoned, although blood transfusions were still helpful in maintaining the plasma protein level, and were unaccompanied by reactions. The last whole blood transfusion was given uneventfully several weeks before her eleventh admission to the Peter Bent Brigham Hospital.

*Immunologic Observations:* To clarify the nature of the sensitivity exhibited by this patient, precipitin tests were set up with the patient's serum and samples of a number of plasma protein fractions,\* including a preparation of albumin to which the patient had shown reactions. Ring tests were used because of the small amount of the patient's serum available for study. The protein fractions were dissolved in normal saline in a concentration of 20 mg./ml. and at higher concentrations to simulate the concentration of albumin employed therapeutically (250 mg./ml.). The test results were read at the end of 24 hours and are recorded in table 1 (columns 1-8). They show the presence of precipitins only to the preparation of concentrated albumin

\* Obtained through the courtesy of Dr. Karl Schmid, Dr. J. L. Oncley and Dr. R. Simpson, Harvard University, Laboratory of Physical Chemistry.

TABLE I  
Precipitin Reactions Before, During and After Treatment

Column	Fraction	Plasma Protein	Preservative or Stabilizer	Diluent	Concentration (mg./c.c.)	Reaction		
						Before	During	After
1	IV and V	Albumin, $\alpha_1$ lipo-, glyco-, and mucoproteins; Zn pptd.	None	0.15M Saline	20	Neg.	N.D.	N.D.*
2	V	Mercapalbumin, 2 samples	None	0.15M Saline	200	Neg.	Neg.	N.D.
3	VI	$\alpha_1$ Acid glycoprotein	None	0.15M Saline	200	Neg.	N.D.	N.D.
4	VI	Glyco-, iodo-, and small soluble proteins	None	0.15M Saline	20	Neg.	Neg.	N.D.
5	IV-7.2	$\beta_1$ metal-binding globulin, Zn pptd.	None	0.15M Saline	110	Neg.	N.D.	N.D.
6	II and III	$\gamma$ globulin. $\beta_1$ lipoprotein, euglobulin	None	0.15M Saline	200	Neg.	N.D.	N.D.
7	II	$\gamma$ globulin	None	0.15M Saline	200	Neg.	N.D.	N.D.
8	V	Albumin previously administered to patients	0.02M Na Caprylate, plus 0.02M acetyl d,l-tryptophanate	0.15M Saline	200	Neg.	N.D.	N.D.
			1/10,000 "Merthiolate"		250	Pos.	Pos.	Neg.
9	V	Albumin, four different preparations		0.30M Saline	250	Pos.	N.D.	N.D.

TABLE I—Continued

Column	Fraction	Plasma Protein	Preservative or Stabilizer	Diluent	Concentration (mg./cc.)	Reaction		
						Before	During	After
10	V	Albumin, Sample HAB-7-2R	0.02M Acetyl d,l-tryptophanate	Water	2.5-250	Pos.	N.D.	Neg.
11	V	Albumin, Sample S-710	0.02M Na caprylate plus 0.02M acetyl d,l-tryptophanate	Water	2.5-250	Pos.	N.D.	Neg.
12	V	Albumin, Sample CD 3554	0.02M Na caprylate plus 0.02M acetyl d,l-tryptophanate	Water	2.5-250	Pos.	N.D.	Neg.
13	IV-7	$\beta_1$ metal-binding globulin	None	0.15M Saline	250	Pos.	N.D.	Neg.
14	V	Ethanol-water precipitated Albumin-recrystallized	None	0.15M Saline	250	Neg.	N.D.	Neg.
			Heated for 1 hour at 60° C.	0.15M Saline	250	Neg.	N.D.	Neg.
			0.2M Na caprylate and 1 hour at 60° C.	0.15M Saline	250	Neg.	N.D.	Neg.
			0.2M Caprylate and 1 hour at 60° C.	0.15M Saline	250	Neg.	N.D.	Neg.
			0.2M Na tryptophanate	0.15M Saline	250	Neg.	N.D.	Neg.
			0.2M Tryptophanate and 1 hr. at 60° C.	0.15M Saline	250	Neg.	N.D.	Neg.
15	"SPPS"	All, except prothrombin, $\gamma$ globulin and fibrinogen	None	Plasma	50	Neg.	N.D.	Neg.
			Heated for 1 hour at 60° C.	Plasma	50	N.D.	N.D.	Neg.

\* N.D.: No precipitin test made.



which had been employed therapeutically. Crystallized mercaptalbumin and fractions similar to Cohn fractions IV and V, but prepared by the newer method of zinc precipitation,<sup>7</sup> did not contain the precipitinogen. On the basis of these observations a program of desensitization was initiated, according to the schedule given in table 2.

TABLE II  
Desensitization Schedule  
Material Used: Salt-Poor Concentrated Human Albumin

Date	Route	Concentration	Amount	Reaction
10/15	Intracutaneous	1/1000	0.1 c.c.	None
	Intracutaneous	1/100	0.1 c.c.	None
	Intracutaneous	1/10	0.1 c.c.	None
	Intracutaneous	Full Strength (25 gm. %)	0.1 c.c.	None
10/16	Intracutaneous	Full Strength	0.1 c.c.	None
	Subcutaneous	1/10	0.1 c.c.	None
	Subcutaneous	1/10	0.2 c.c.	None
	Subcutaneous	1/10	0.3 c.c.	None
	Subcutaneous	Full Strength	0.1 c.c.	None
	Subcutaneous	Full Strength	0.2 c.c.	Patient complained of itching; no local reaction
10/17	Subcutaneous	Full Strength	0.1 c.c.	None
	Subcutaneous	Full Strength	0.2 c.c.	None
	Subcutaneous	Full Strength	0.3 c.c.	None
	Intravenous	1/10	0.1 c.c.	None
	Intravenous	1/10	0.2 c.c.	None
	Intravenous	1/10	0.3 c.c.	Two hives developed; Benadryl 100 mg. given and reaction stopped
10/18	Subcutaneous	Full Strength	0.3 c.c.	None
	Intravenous	1/10	0.2 c.c.	None
	Intravenous	1/10	0.3 c.c.	None
	Intravenous	1/10	0.4 c.c.	None
	Intravenous	1/10	0.5 c.c.	Patient complained of small chill and feeling warm; Benadryl for hives
	Intravenous	1/10	0.5 c.c.	
10/19	Intravenous	1/10	0.2 c.c.	None
	Intravenous	1/10	0.5 c.c.	None
	Intravenous	1/10	0.7 c.c.	None
	Intravenous	1/10	1.0 c.c.	None
	Intravenous	1/10	2.0 c.c.	None
10/20	Intravenous	Full Strength	35 c.c.	None: as 2-3 c.c. lots during whole day
10/21	Intravenous	Full Strength	100 c.c.	None
10/22	Intravenous	Full Strength	100 c.c.	None
10/24	Intravenous	Full Strength	40 c.c.	None
10/27	Intravenous	Full Strength	100 c.c.	None
10/31	Intravenous	Full Strength	160 c.c.	None

The albumin used was obtained from a lot to which the patient was known to be sensitive. Following the intravenous injection of 7.5 mg. albumin in 0.3 ml. water on October 17, typical hives appeared which were controlled by Benadryl. The program was consequently altered on the subsequent day, beginning with a subcutaneous dose of 75.0 mg. of albumin; thereafter, a dose similar to the hives-inducing one was

attained without event. A similar episode occurred following the intravenous injection of 12.5 mg. albumin in 0.5 ml. water. The program was continued and no further reactions appeared. A serum sample taken on October 18, after three days of desensitization, gave a diminished precipitin reaction, as shown in table 1, column 8. After five days of desensitization the patient's serum no longer contained demonstrable precipitins to any plasma protein, and she was able to tolerate 8.0 gm. of albumin in 25 per cent concentration over the course of one day without reaction. She was then given an additional 125 gm. of 25 per cent salt-poor albumin over the next six days without reaction, and was discharged on a program consisting of an infusion of 25 gm. of albumin every seven days. A letter received 25 days after her discharge indicated that the infusions were being given weekly and were attended by no urticarial or febrile reactions. Three months later the patient was again seen because of the development of reactions to the albumin infusions, consisting of headaches and perspiration, unaccompanied by urticaria. Her serum was examined for precipitins, using the preparation of albumin to which she had formerly reacted positively (table 1). No precipitins were found. There were no precipitins to a new Stable Plasma Protein Solution (SPPS, table 1), which consists of normal plasma from which prothrombin,  $\alpha$ -globulin and fibrinogen have been removed.<sup>8</sup> She was given several infusions of this material, without reactions, although the relatively high salt content of this particular preparation rendered it less suitable for the treatment of her edema.

#### DISCUSSION

After the patient's serum was shown to contain precipitins to preparations of concentrated albumin, the problem remained to identify the specific offending agent. The following possibilities existed:

1. The patient was sensitive to a normal component of plasma proteins. That this was unlikely is evidenced by the fact that a few weeks before the eleventh admission a whole blood transfusion was given with no reaction. Also, fractions IV and V, similar to Cohn fractions but prepared according to an improved method for the separation of protein components, contained albumin which did not react with the patient's serum (table 1, columns 1 and 2).

2. A preservative or stabilizer added to the albumin had formed an antigenic complex with the albumin. This was unlikely, since the patient had used preparations of albumin stabilized with acetyltryptophanate until the winter of 1949-1950, and had then changed to preparations containing caprylate, with no change in her reactions. Furthermore, one lot of material used by the patient in 1951 contained both caprylate and acetyltryptophanate. Finally, the patient's serum before desensitization reacted with lots of albumin prepared in 1944 containing Merthiolate as a preservative, and no acetyltryptophanate or caprylate, whereas it did not react with recrystallized albumin with added tryptophanate or caprylate (table 1, columns 9 and 14).

3. The patient was sensitive to some denatured plasma protein which was present in trace quantities in albumin prepared by the standard method of ethanol fractionation, but absent from material prepared by the zinc method as well as from recrystallized mercapalbumin. None of the studies shown above identify such a substance. Further studies (by Dr. David Gitlin, of the Children's Medical Center) on sera obtained before and after desensitization (table 1, columns 10-14) corroborated the findings that prior to treatment there were precipitins present in the patient's serum to commercial preparations of concen-

trated albumin and none to recrystallized serum albumin. In addition, a positive precipitin reaction was obtained with a 25 per cent saline solution of fraction IV-7, which contains chiefly beta metal-binding globulin, but also albumin,  $\alpha$ -globulin and other proteins in small amounts (table 1, column 13). Both of these reactions disappeared after desensitization. Hence it appears likely that the patient was reacting to a substance present in small amounts, quite possibly a denatured protein.

#### SUMMARY

A case is reported of idiopathic hypoproteinemia complicated by acquired sensitivity following repeated injections of standard preparations of human serum albumin, totaling approximately 4,750 gm. On the basis of immunologic studies, the offending antigen is thought to be a substance, possibly denatured protein, present in concentrated salt-poor human albumin and in preparations of fraction IV-7. Desensitization led to disappearance of the precipitin from the serum, and cessation of the febrile and urticarial responses to albumin; allergic sensitivity did not reappear as long as the patient received regular injections of albumin thereafter. Albumin prepared according to the newer methods of plasma fractionation as well as recrystallized albumin was free of the precipitating substance; that prepared by the ethanol-water method of fractionation was not.

#### ACKNOWLEDGMENT

It is a pleasure to acknowledge the generous help of Dr. George W. Thorn, Dr. Charles A. Janeway and Dr. David Gitlin in the preparation of this manuscript. We are also indebted to Dr. Thorn for making the patient available for study.

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## WEIGHT REDUCTION IN AN OBESE DIABETIC\*

By JANET R. KINNEY, M.D., *Chicago, Illinois*

THE relationship of metabolic and psychogenic factors in diabetes is illustrated graphically by the following case history.

## CASE REPORT

A 46 year old white female was seen in the diabetic clinic of St. Luke's Hospital on December 31, 1943, as a problem in diabetic management. She had noted the onset of polyuria, polydipsia and dryness of the mouth in 1941. In two years of clinic management her weight and insulin requirements had steadily risen. She now weighed over 300 pounds, and her insulin dosage was 90 units protamine zinc insulin and 90 units of regular insulin. The blood sugar was 378 mg. per cent, and urinalysis showed a 4 plus glycosuria.

The patient complained bitterly of pain in her knees and inability to cope with her daily work. She had weighed 116 pounds at 18 years, 150 pounds at 24, and 200 pounds at 36. She attributed her steady increments in weight to her pregnancies. She was a gravida VI, para V; none of her babies had weighed over seven pounds. The menopause had occurred at 36. A maternal aunt had had diabetes. Her average diet was, "No breakfast; for lunch a sandwich; for dinner a serving of meat, a slice of bread, vegetables, and a pot of tea."

On physical examination this patient was five feet tall, with small delicate hands and feet and trim ankles; but the remainder of the framework was lost in folds and aprons of 300 pounds of fat. The blood pressure, determined with difficulty, was 110/60 mm. of Hg. The eye grounds were normal and without exudates or hemorrhages. The heart tones and breath sounds were heard distantly, but the chest film revealed a normal cardiac contour and clear lung fields. Pendulous folds of fat prevented adequate abdominal examination. In the extremities the arterial pulsations and reflexes were normal, but the arches of the feet had flattened and the knees had buckled.

The patient was hospitalized and stabilized on a diet of carbohydrates, 90 gm.; protein, 60 gm.; fat, 40 gm., with 80 units of protamine zinc insulin. While she was in the hospital the basal metabolic rate was plus 9 per cent, the sella turcica was normal, and the electrocardiogram was within normal limits.

Figure 1 shows the course of the next five years, in which her weight was reduced by half and her insulin from 180 units to none.

Although at weekly clinic visits the patient was coöperative but reticent, as time went on each visit unfolded problems—a son in the landing at Cassino, a daughter's marriage, the youngest child's pneumonia, the teen-ager's "hot rod."

At one visit the patient was asked why she was now able to lose weight, and with better insight than her physician's she replied, "I can talk now. I used to just boil inside, and then when I thought I would explode I'd go out and eat and eat—not just a soda but two or three, and a pound of candy. Then I'd be so ashamed and go back home and try hard. Then when I came to the clinic nobody would believe that I tried. When I found I could come and talk, I could let it out and I didn't have to eat. That kind of eating is like drinking. Once when you said I could come in two weeks instead of one, I was scared. I knew I couldn't go two weeks

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From the Department of Medicine, University of Illinois.

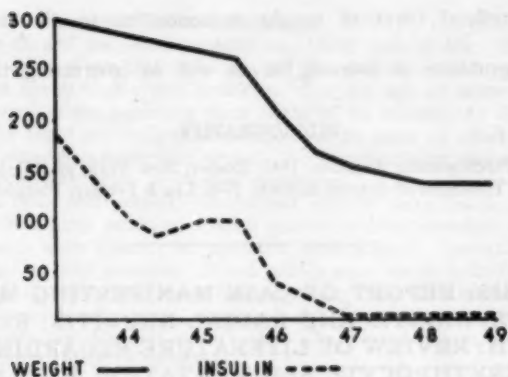


FIG. 1. Parallel reduction in weight and insulin.

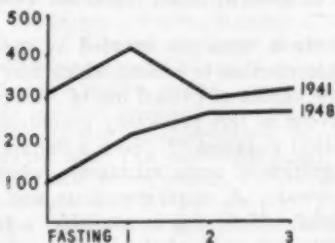


FIG. 2. Glucose tolerance curves in 1941 and 1948.

without talking." Then she added proudly, "Now I don't have to come in to talk. I can talk it out with myself. I guess I am growing up."

#### DISCUSSION

In this case food was an oral satisfaction for the release of tension and anxiety. Until the basic problem of finding other releases for these tensions could be solved, no dietary plan could be successful. When this adjustment was made the patient followed her diet and lost weight. With the loss of weight she began to take an interest in many activities which she formerly had been unable to perform. Her great pride was that she was able to garden and grow all her own vegetables.<sup>1</sup>

Loss of weight was paralleled by reduction in insulin requirements.<sup>2</sup> Figure 2 shows the glucose tolerance curves after 100 gm. of glucose orally; in 1941 at the time of the discovery of her diabetes, and in 1948 when she had been controlled for nine months without insulin.

#### SUMMARY

1. This case illustrates the importance of the control of the mechanism of overeating in the dietary management of the obese diabetic.

2. The beneficial effect of weight reduction on insulin requirement is illustrated.

3. The importance of listening to as well as instructing the patient is emphasized.

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### TRICHINOSIS: REPORT OF CASE MANIFESTING MYOCARDITIS, ENCEPHALITIS AND RADIAL NEURITIS; RESPONSE TO ACTH; REVIEW OF LITERATURE REGARDING THE ERYTHROCYTE SEDIMENTATION RATE\*

By DAN C. ROEHM, M.D., Nashville, Tennessee

WHEN the human body is massively invaded by the larvae of *Trichinella spiralis*, a violent systemic reaction is evoked which may lead to death within several weeks.<sup>1</sup> With the advent of clinical use of ACTH and cortisone it has become possible to intervene in this previously uncontrollable sequence and to preserve life in these critical instances.<sup>2-4</sup> Such a therapeutic possibility makes urgent the prompt recognition of acute trichinosis, whose manifestations are, however, exceedingly protean. A more immediate and conclusive laboratory procedure would be helpful. Until this is available, a high degree of clinical awareness must be maintained, particularly in the case where overwhelming involvement jeopardizes life.

#### CASE REPORT

A 34 year old bachelor carpenter was admitted to the hospital on September 28, 1952, in a state of amnesia. A brother who accompanied him was the informant.

Three weeks prior to admission the patient developed nausea and vomiting, followed in several days by watery diarrhea. In the second week of illness burning of the eyes became quite severe, and a physician administered penicillin for "conjunctivitis." Swelling then developed about the eyes as well as the hands and feet. Vomiting had ceased by this time, but diarrhea remained intractable. Finally, several days before admission, the patient had evidenced extreme weakness and loss of memory. Another physician saw the patient briefly on the day of admission to establish the need for immediate hospitalization, and informed the brother that the patient's appearance suggested glomerulonephritis.

The past medical history indicated that the patient had been treated for combat fatigue for a short time in 1944 but had fully recovered. The feature of his social history considered most significant was that, being a bachelor, he was in the habit of eating his meals at various small restaurants and roadside inns. Owing to his amnesia for recent events, he could not recall having been served improperly prepared pork.

\* Received for publication August 19, 1953.

From the Medical Service, Thayer Veterans Administration Hospital, and the Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee.



**Physical Examination:** The temperature was 101° F., the pulse was 110, respirations were 16 and the blood pressure was 95/65 mm. of Hg. The patient was an acutely ill, dazed white male who gripped the examining table with both hands in order to sit upright. He was unable to state his age or home address, or to recount the events of the preceding three weeks of his illness. At times he laughed weakly when he could not reply satisfactorily, but he made no effort to confabulate. There was no outspoken periorbital edema. No petechiae were observed in the skin, nail beds, conjunctivae, fundi or mucous membranes. The neck was supple. There was no lymph node enlargement. Occasional rhonchi were heard. Coughing, incident to deep breathing, produced a small amount of blood-streaked mucoid sputum. The heart sounds were distant; no murmurs were present. Generalized abdominal pain was elicited on deep pressure. Bowel sounds were not remarkable. All muscles were found to be surprisingly weak but were completely free of tenderness. Respiratory motions did not appear compromised. Aside from the sensorial defect, neurologic examination was not remarkable. The clinical impression on admission was that trichinosis should be excluded.

**Laboratory Studies:** A direct eosinophil count revealed 12,525 cells per cubic millimeter. The total white count was found to be 18,850; the differential: eosinophils, 76 per cent; neutrophils, 18 per cent; lymphocytes, 4 per cent; monocytes, 2 per cent. Hemoglobin was 16 gm. per cent; hematocrit, 51 vol. per cent; platelets, 120,000 per cubic millimeter. A search for larval forms of *Trichinella spiralis* in laked venous blood, in the centrifugate of 10 c.c. of spinal fluid, in the urinary sediment, and in the blood-tinged sputum yielded negative results. The diagnosis of acute trichinosis therefore remained presumptive.

The following values were obtained on specimens secured prior to therapy: non-protein nitrogen, 31 mg. per cent; CO<sub>2</sub> combining power, 57 vol. per cent; serum chloride, 536 mg. per cent; total serum protein, 4.8 gm. per cent; albumin 3.1, and globulin, 1.7 gm. per cent; uric acid, 3.4 mg. per cent; glucose, 124 mg. per cent; serum bilirubin, 0.3 mg. per cent; alkaline phosphatase, 3.8 units (King-Armstrong); cephalin flocculation 4 plus at 48 hours; thymol turbidity, 3.0 units; total cholesterol, 140 mg. per cent, with ester of 60 mg. per cent; serum calcium, 9.5 mg. per cent, and phosphorus, 3.6 mg. per cent; serum sodium, 134 mEq./L. Serum potassium specimen showed hemolysis, a second specimen 24 hours later, after administration of 3.0 gm. of KCl, contained 3.5 mEq./L. Blood Kahn was negative. Spinal fluid: protein, 52 mg. per cent; negative mastic; no increase in cells; pressure, 180 mm. Urine: specific gravity, 1.025; numerous granular casts and red blood cells per high power field; 1.5 gm. of protein excreted in first 24 hours. A blood culture was sterile.

**Clinical Course:** Six hours following admission the patient's condition suddenly became critical: the temperature rose to 103° F. and the pulse to 140, while the blood pressure fell to 80/60 mm. of Hg. He was unable to move any extremity, and was incontinent and disoriented. At this point an intravenous infusion containing 20 mg. ACTH and 40 mEq. KCl was started (figure 1). At the conclusion of this eight hours later, all evidence of acute toxicity had disappeared. He requested and was fed breakfast, and swallowed enteric-coated tablets of KCl. An aqueous suspension of ACTH was then begun intramuscularly in 10 mg. doses every six hours. Nevertheless, shortly after nightfall, his temperature rose to 103.6° F., and he talked with unseen persons, sang, laughed and cried weakly. A second course of intravenous ACTH was as successful as the first. A third episode similar in all essentials on the third day necessitated the last intravenous course of ACTH. Although an elevation to 102° F. occurred on the fifth day, this was unattended by delirium or prostration, and no additional measures were instituted.

At a time of great muscular weakness the patient was found to have a vital capacity of 3.2 L. Clinical signs of congestive failure were never observed, and chest

x-rays revealed no cardiac dilatation, pulmonary vascular engorgement or pneumonitis.

The day following admission *Trichinella* antigen was administered intradermally. Readings at 20 minutes, and at 24 and 48 hours were negative. A sternal marrow aspiration on the second day exhibited granulocytic preponderance, particularly of eosinophils, but no larvae were recovered. However, a muscle biopsy the same day revealed numerous larval forms identified as *T. spiralis* (figure 2a).

On the fourth hospital day complete left wrist drop developed. This was splinted, and eventually normal strength was regained. By the sixth day, fever had disappeared and intramuscular ACTH was also discontinued, without evidence of adverse

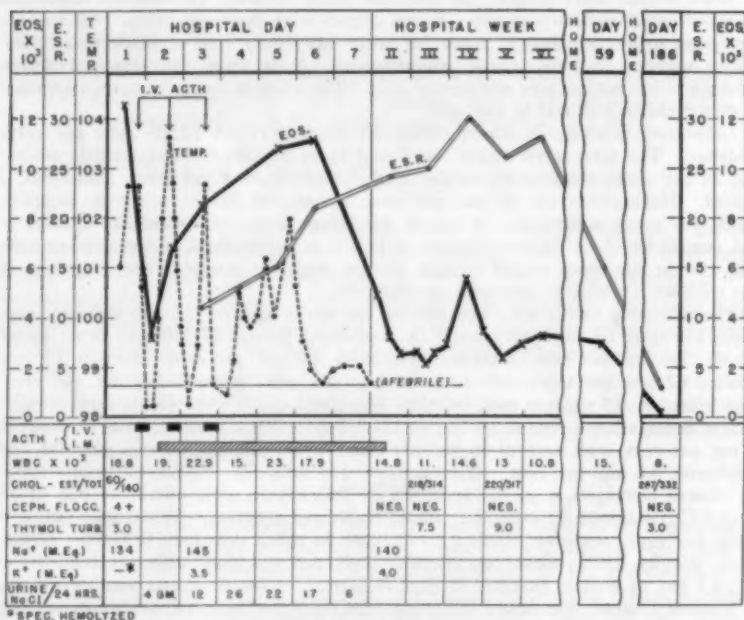


FIG. 1. Relationships between number of circulating eosinophils, temperature, erythrocyte sedimentation rate (ESR) and ACTH therapy. Note relatively normal ESR during early anaphylactic phase with rise in convalescence, chloride diuresis during ACTH administration.

effects from this withdrawal. The initial amnesia and episodes of delirium gave way to patient discouragement and apathy when the devastating nature of his illness could be fully comprehended. At night he was invariably restless and required sedation. After a period of two weeks of little improvement, muscle function began to return fairly rapidly. After intensive physiotherapy, he was discharged on the forty-fifth hospital day and returned to his trade without restrictions.

**Additional Clinical and Laboratory Studies:** An electroencephalogram obtained on the eighteenth day, considerably after the stormy phase had been passed, exhibited only mild irregularities and pointed to no cortical dysfunction (classification: B-3). A tracing at six months was entirely normal.

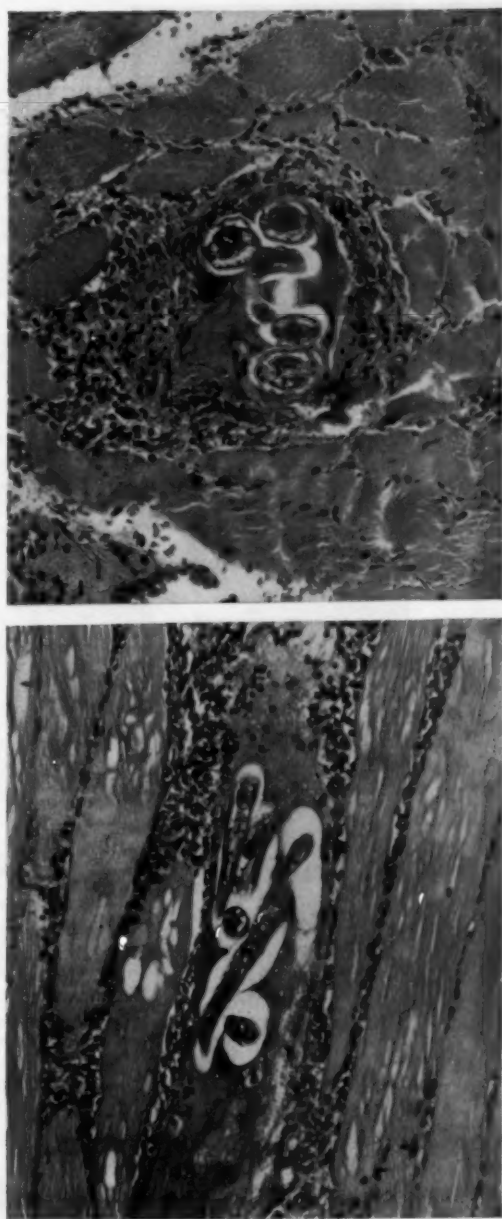


FIG. 2. Muscle biopsy sections (approximately  $\times 200$ ).

a. 9/29/52 Tangential and cross sections of uncoiled larval form (possibly two) surrounded by intense inflammatory infiltration which is preponderantly eosinophilic but also contains monocytes and lymphocytes. Muscle fiber coagulation in some areas.  
b. 10/16/52 Larva of distinctly greater size. Hyaline capsule formation. Mononuclear cells predominate in exudate.

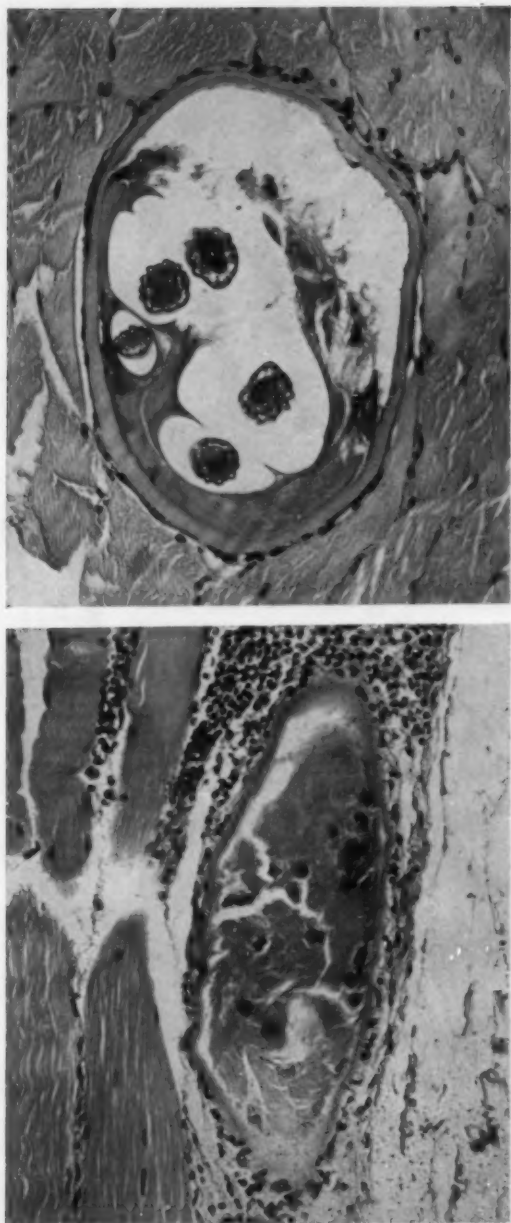


FIG. 2.—Continued.

c. 11/25/52 Capsule seen longitudinally, illustrating characteristic oval shape. Cells within are probably histiocytes, which occasionally succeed in killing larva. However, in this instance serial sections demonstrated an intact parasite.

d. 4/1/53 Larva well encapsulated at six months. Inflammatory reaction has disappeared.

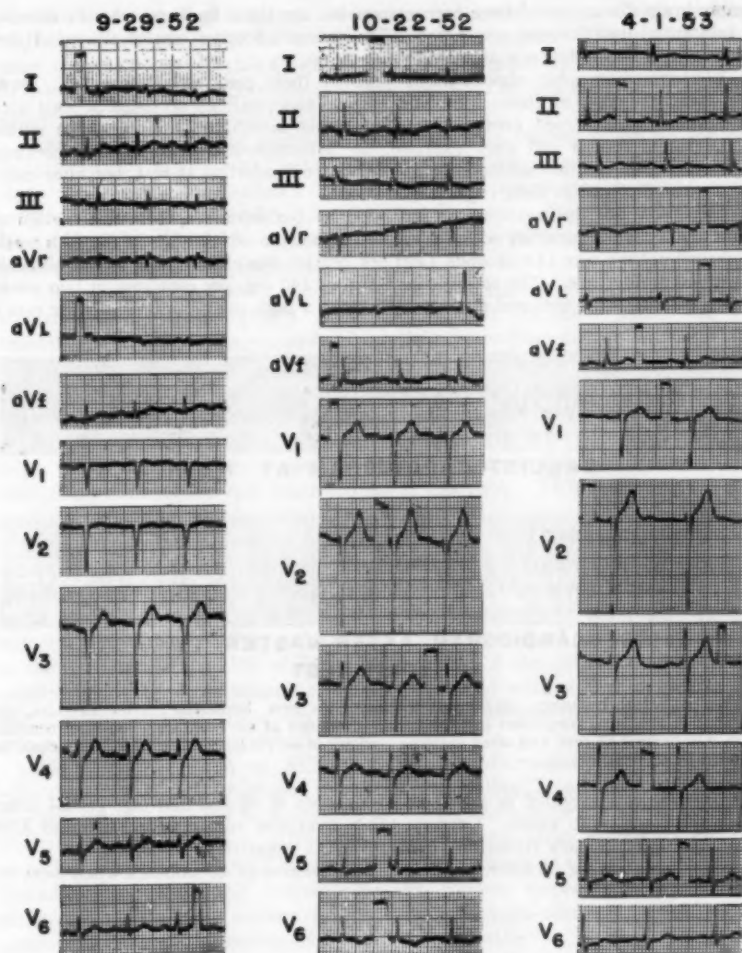


FIG. 3. Electrocardiograms, 1, 26 and 186 days following first admission. Most striking features are, successively, low voltage, T-wave inversions, and eventual reversion to a tracing that falls within normal limits at six months.

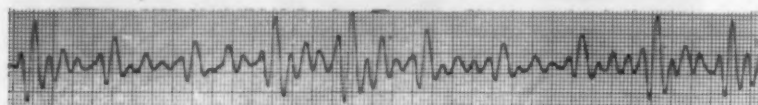
Psychologic testing\* during the third week of hospitalization revealed an average level of intelligence. However, although his pre-illness abilities were necessarily unknown, his performance abilities were significantly lower than verbal ones, and ability to learn and synthesize new material was retarded. It was concluded that

\* Wechsler-Bellevue Adult Intelligence Scale, Form I, Bender Gestalt, Goldstein-Scheerer, Kohs Blocks, and the Eisensen Aphasia Test were administered by Irving Bialick, Ph.D.

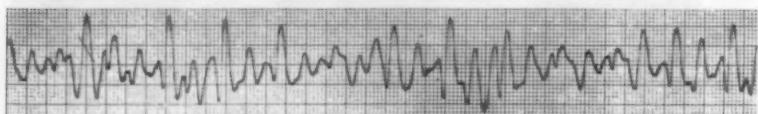
organic brain disease could have been responsible for these findings. At six months, no substantial improvement was noted. The patient's brother was of the belief that mentality had been adversely affected by his illness.

Electrocardiographic abnormalities reached their peak on October 22, seven weeks after the onset of illness. ST and T-wave abnormalities persisted at least until the eleventh week record (not shown), but at six months all findings were within normal limits at rest and after exercise. A ballistocardiographic tracing obtained six months after the first admission was considered borderline at rest, but after exercise abnormality was evident (figure 4).

Hepatocellular dysfunction was indicated by the initial cephalin flocculation of 4 plus and a thymol turbidity which reached a maximum of 9.0 units in the fifth week. Prothrombin time was 13.4 seconds (100 per cent). No elevation of serum bilirubin was found at any time. The serum cholesterol of 140 mg. per cent rose in two weeks to over 300 and was sustained at six months with a high ester fraction (86 per cent).



BALLISTOCARDIOGRAM AT REST



BALLISTOCARDIOGRAM AFTER MASTER TWO-STEP EXERCISE TEST

FIG. 4. High-frequency, undamped tracings. At rest, borderline; after exercise, appearance of abnormal complexes in expiration. Obtained at six months, when electrocardiogram was normal at rest, and after exercise, and when no evidence of heart disease could be detected by clinical means.

Creatine was excreted in the urine in amounts of 96 and 128 mg. per 24 hours in the third and ninth weeks. Corresponding creatinine values were 1,040 and 2,700 mg. A test for urinary ribose on October 14 was negative.\*

A skin test using *Trichinella* antigen was positive in 20 minutes when next repeated at six months.

#### DISCUSSION

The presenting clinical picture was dominated by symptoms arising from the central nervous system. The confusion and amnesia were seen to be reminiscent of Korsakoff's syndrome. This association has been described in the past,<sup>8</sup> and more recently the similarities of trichinous encephalitis and this syndrome have been reemphasized.<sup>6</sup> *Trichinae* may become situated within the brain substance in granulomatous nodules,<sup>9</sup> and subsequent calcifications have been incriminated as the cause of epilepsy.<sup>7</sup> Peripheral nerve paralysis, presumably a toxic effect, may be the presenting complaint in trichinosis.

\* This test was performed through the kindness of Dr. A. S. Minot, of the Department of Medicine, Vanderbilt University School of Medicine.



The sequence of gastrointestinal symptoms, conjunctivitis, edema, weakness and mental collapse led to the consideration of trichinosis. The finding thought most inconsistent with this diagnosis was the complete absence of muscle pain or tenderness. (Pain perception was intact.) Yet this may be encountered despite the intense inflammatory process.<sup>3</sup>

On the day following admission a stool was examined at length for adult or larval forms of trichinae, with negative results, as is usually the case at this stage. Because of the patient's debilitated state, it was elected not to administer purges in an effort to dislodge possible remaining adults from the small intestine. These forms have been demonstrated in this location in human beings at autopsy as long as 54 days after ingestion.<sup>8</sup>

The myocarditis of acute trichinosis, the most serious complication, has been well described morphologically.<sup>9</sup> Encystment does not occur within the heart muscle, but larvae may be recovered from the myocardium during the acute stage. Whether the myocarditis stems from the actual presence of the non-encysted larvae within the myocardium or from the toxemia is controversial. In the present case, myocarditis reached its maximal intensity, as judged electrocardiographically, in the seventh week of illness (fourth week of hospitalization), when fever and the severest skeletal muscle manifestations had abated. However, the sedimentation rate was maximal at this time. This evident delay of the peak of myocarditis is somewhat characteristic.<sup>1</sup>

Recovery without sequelae is the general rule in trichinous myocarditis, as far as can be determined clinically and electrocardiographically.<sup>10, 11</sup> However, the ballistocardiograph, which derives closely from the mechanical force of the heart beat, should afford a particularly useful evaluation of the completeness of myocardial recovery. This method has not been utilized in published reports to date. The abnormality of figure 4, in view of the previous electrocardiographic evidence of myocarditis, may be ascribed with a fair degree of certainty to the foregoing trichinous myocarditis in a 34 year old normotensive with no symptoms of coronary insufficiency.

After administration of ACTH, a chloride diuresis occurred (figure 1) which reached a peak of 26 gm. per 24 hours (as NaCl) on the fourth hospital day and which could not be accounted for on the basis of better alimentation and electrolyte administration. Although contrary to the more customary chloride-retaining properties of ACTH, such a diuresis occurs at the onset of recovery from the serum sickness,<sup>12</sup> a disease similar in many respects to acute trichinosis.<sup>13-15</sup> Experimental studies suggest that the myo-edema of trichinosis is accompanied by the retention of sodium and chloride.<sup>12</sup>

The low serum protein value on admission (4.8 gm. per cent) is seen in certain of the severe cases of trichinosis,<sup>16, 17</sup> and may be a reflection of increased membrane permeability, with resulting protein loss from the vascular compartment. However, this degree of increased permeability has not been unequivocally demonstrated in animal studies.<sup>18</sup> Hepatocellular damage may also play a part. An apparent depression of serum proteins on the basis of hemodilution is excluded as a cause by the narrow range of the hematocrit and hemoglobin values (49 to 51 vol. present, and 15 to 16 gm. per cent, respectively) during the first week.

The lymphopenia (4 per cent) present on admission was possibly indicative

of increased corticoid production and is only a relatively constant finding.<sup>1</sup> Undoubtedly, hormone therapy continued this depression, as no value greater than 10 per cent was observed during exhibition of ACTH. Two days following its discontinuance, this rose to above 20 per cent, where it remained. The resistance of the eosinophilia to continued hormone administration is not exceptional in human infection<sup>2-4, 16</sup> or in animal studies.<sup>4</sup>

The earliest erythrocyte sedimentation rate values were probably not influenced by ACTH, the first determination having been made 36 hours after commencement of therapy; in any event, the erythrocyte sedimentation rate rose slowly despite its continued administration. Blood fibrinogen was not determined. Low or normal levels might have explained the relatively normal rates, since some form of hepatocellular damage was sustained.

#### THE ERYTHROCYTE SEDIMENTATION RATE (ESR) IN TRICHINOSIS

Procedures that are diagnostic in acute trichinosis (other than biopsy) require several weeks for the development of demonstrable antibodies.<sup>1</sup> By this time the issue of recovery or death may have been settled. Although eosinophilia has often betrayed the presence of trichinae to the clinician, this finding may be lacking, particularly in the most desperate cases. Another simple hematologic examination may also be of inferential value in acute trichinosis but has not received the attention it may deserve. The observation of the ESR to be only minimally elevated during the fulminating stage of the present case was unexpected.

The literature on trichinosis has been reviewed with respect to this test since 1920, when it had assumed some degree of usage. The large majority of case reports, although replete with other hematologic data, fail to include this parameter. However, observations were recorded in 38 individual case reports and in four works summarizing findings in 782 patients in large epidemics. Little elevation of the ESR was noted in the majority of instances (table 1).

The occurrence of relatively normal values of the sedimentation rate in acute trichinosis has been commented upon by several observers,<sup>42, 26, 25</sup> but no attempt has been made to account for this somewhat anomalous finding except in cases in which congestive failure was felt to be responsible.<sup>22, 23</sup>

It is impossible to reduce to common values the figures obtained by the various methods of determination. Nevertheless, as seen in table 1, the ESR, determined by whatever method and often late in the course of the illness, is 25 mm./hour or less, a figure often considerably exceeded by acute infectious diseases,<sup>42</sup> in 79 per cent of the cases of uncomplicated trichinosis. Sixty-eight per cent are 25 mm./hour or less if individual cases are included with obvious complications known to elevate the ESR. Eosinophilia (> 6 per cent) is present in 86 per cent of the uncomplicated and in 84 per cent of the entire group of collected individual reports at the time of the recorded ESR.

When the anaphylactic nature of acute trichinosis is considered, an explanation of the relatively normal ESR, particularly during the early stages, appears to be at hand. Studies regarding the ESR in hypersensitive states of various origins have revealed a high percentage of normal<sup>43-48</sup> or decreased<sup>49</sup> rates in allergic diseases uncomplicated by infection. An elevated ESR may even be

TABLE I

The ESR Recorded in the Literature, 1920-1952, in Acute Trichinosis \*

## A. Case Reports of Uncomplicated Trichinosis

Ref.	No.† Cases	ESR	Day of Illness	Severity	Eosinophilia	Misc.
19	1	4	14th	Mild	+	—
20	1	6	14th	Severe	+	—
21	1	25	14th	Fatal	—	Eventual aplastic anemia
22	RE 1	.3/min.	20th	Fatal	—	Carditis C.H.F.‡
23	1	"Not elev."	—	Fatal	—	Carditis C.H.F.‡
24	1	21	22nd	Severe	+	—
25	(8) 3	21 18 11	21st 16th 23rd	Moderate	+	—
18	WG 1	64	21st	Severe	+	Carditis
26	4	Normal (2) Mod. incr. (2)	Acute phase	Moderate and severe	+	—
57	W 1	24	42nd	Fatal	—	Carditis C.H.F.‡
27	6	Normal (3) Mod. incr. (3)	Acute phase	Mild	+	—
28	WG 1	30	15th	Moderate	+	Carditis
29	1	17	18th	Moderate	+	—
30	WG 1	26	11th	Moderate	+	—
	WG 1	60	18th	Moderate	+	—
31	W 1	39	24th	Severe	+	Carditis
I	RE 1	1.2/min.	35th	Fatal	+	—
Author's 1st case	W 1	11	21st	Severe	+	—

\* A. Of 28 individual cases of uncomplicated trichinosis, in 22 (79%), the earliest ESR recorded did not exceed 25 mm./hour. Eosinophilia was present at time of the recorded ESR in 24 (86%). B and C. Of 10 cases with co-existing complications which alone would normally elevate the ESR, in 4 this did not occur. A, B, and C. In all 38 individual reports, the ESR did not exceed 25 mm./hour in 26 (68%), while eosinophilia was present in 32 (84%). However, in four fatalities, eosinophilia was absent when the ESR finding was present. D. The ESR in four large epidemics comprising 782 patients. Relatively low ESR's were obtained in comparable percentages.

† Method employed in determining ESR when stated: WG—Westergren; W—Wintrobe, corrected; RE—Rourke-Ernstene; (8)—upper limit, unspecified method.

‡ Congestive Heart Failure.

TABLE I—Continued

## B. Trichinosis with Complication, Not Increasing ESR

Ref.	No.† Cases	ESR	Day of Illness	Severity	Eosino- philia	Complication
32	1	14	7th	Moderate	+	Immediately post partum
33	WG 1	22	42nd	Moderate	—	Mumps; nonfatal periarthritis
34	WG 1	8	18th	Severe	+	Purulent sinusitis
Author's 2nd case	W 1	20	14th	Mild	+	Strep. tonsillitis, rising A-S titer

## C. Trichinosis with Complication, Probably Increasing ESR

Ref.	No.† Cases	ESR	Day of Illness	Severity	Eosino- philia	Complication
35	2	"Complete"	7th	Severe	+	Periarthritis nodosa
		"Complete"	30th	Fatal	+	Periarthritis (cause of death)
36	1	"Elev."	60th	Severe	—	Hepatitis, dermatomyositis
37	W 1	34	6th	Moderate	+	Psoriasis with lymphadenopathy
38	1	33	14th	Moderate	+	Pneumonitis with leukopenia
39	WG 1	120	21st	Moderate	+	Loeffler's syndrome

## D. ESR Data in Four Large Epidemics

Ref.	No. Cases with ESR	Method	Day of Illness	Severity	Summary of ESR Observations
40	70	Westergren	14th–21st	Mild	"55%" of cases showed ESR <15 mm./hour. Tests repeated occasionally.
41	55	Westergren	ca. 21st	Mild	Average value of ESR in entire series = 7.5 mm./hour. (Range not given.)
42	40	Fåhræus	3rd–89th	Mild to severe	"77%" of cases showed ESR <20 mm./hour on repeated testing.
11	617	—	7th–180th	Mild 294 Mod. 212 Sev. 111	ESR "normal in almost all . . . (uncomplicated) cases . . . even with persistent fever." (No figures given.)

lowered during the course of an infectious disease with the onset of serum sickness,<sup>50-53</sup> the mechanism probably being a reduction in fibrinogen.<sup>54, 55</sup> No data are available as to fibrinogen levels in acute trichinosis.

If, as Cutler states, "essentially the sedimentation phenomenon depends upon the amount of cell destruction going on in the body,"<sup>56</sup> the disease under consideration at present is a noteworthy exception. It seems permissible to speculate that in the acute stage of trichinosis, the allergic feature exerts a stronger retarding influence on the sedimentation of red cells than the accelerating action derived from the widespread tissue destruction. Encountering a relatively normal ESR, although a "negative" finding, in the midst of this acutely wasting disease should be considered to have a positive significance.

The delayed rise in the ESR in the fifth week of illness of the present case is unexplained, although a very close correlation with the myocarditis was noted. In testing this as a possible mechanism, of the six individual cases (table 1) free of extrinsic complications but exhibiting elevated ESR's, myocarditis (without resulting failure) was a conspicuous finding in three. Thus it is conceivable that when unattended by failure, myocardial inflammation, which is unique in trichinosis in that the organisms are expelled from this site, may considerably elevate the ESR, in contrast to skeletal muscular inflammation, where the larvae remain.

#### SUMMARY AND CONCLUSIONS

1. An instance of acute trichinosis is reported which exhibited myocarditis, encephalitis and radial neuritis, in addition to the customary myositis.
2. ACTH, administered intravenously, rapidly terminated three crises in a persuasive manner. It was clear, however, that this therapy, three weeks after the onset of symptoms, did not prevent permanent injury to the brain and very likely to the heart as well.
3. A review of the literature with respect to the erythrocyte sedimentation rate (ESR) indicates that often relatively normal values occur, particularly in the acute uncomplicated disease. It is probable that the relatively low ESR is an integral portion of the hematologic response in acute trichinosis, as is eosinophilia, and is a manifestation of the serum-sickness-like nature of the illness. When the hypersensitive stage has passed a delayed elevation may occur, as in the present case.
4. In four of the published reports of fatalities, when the eosinophils had disappeared from the peripheral blood, the ESR finding remained as the only hematologic indication of the allergic nature of the underlying disease.
5. Encountering a relatively low ESR in a clinical syndrome suggesting inflammation and tissue destruction may, on occasion, lead to the proper consideration of acute trichinosis.

*Note:* A subsequent case, confirmed by biopsy, exhibited tonsillitis from which beta-hemolytic streptococci were cultured. The anti-streptolysin titer rose from 50 to 166 Todd units in 11 days, while circulating eosinophils fell progressively from 7,600 to 3,900 per cubic millimeter. During this period, serial ESR determinations were: 20, 20, 16, 14 and 16 mm./hour, indicating that the ESR may not necessarily reflect the presence of secondary bacterial infection in acute trichinosis. A delayed elevation of the ESR did not occur, and no evidence of myocarditis was found by the means employed in the above case.

## ACKNOWLEDGMENT

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### SPONTANEOUS PARTIAL OCCLUSION OF THE INNOMINATE ARTERY: REPORT OF A CASE WITH ANGIO-CARDIOGRAPHIC CONFIRMATION \*

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THE clinical syndrome of carotid artery occlusion with resultant cerebral vascular insufficiency is well recognized, having been emphasized as long ago as 1914 by Hunt<sup>1</sup> and more recently reviewed by Galdston and his associates.<sup>2</sup> There are varied etiologic factors. Carotid arteriosclerosis with superimposed thrombosis is thought to be the commonest offender,<sup>2</sup> while trauma,<sup>1</sup> "serpentine" aneurysms<sup>3</sup> and embolization<sup>1,2,4</sup> have also been implicated. Signs of optic nerve damage on the side of the thrombosed vessel occurring together with contralateral hemiplegia should arouse suspicion of carotid artery occlusion.<sup>5,6</sup> Carotid angiography may confirm the clinical impression.<sup>7</sup>

Disease of more proximal vessels, the aorta and innominate, has been described with associated or secondary carotid artery obstruction. Aortic aneurysm,<sup>2,8</sup> syphilitic aortitis and arteritis with<sup>9</sup> and without<sup>2</sup> aneurysm, and dissecting aortic aneurysm with innominate and carotid involvement<sup>10</sup> have all been reported. According to Adams<sup>11</sup> and Moersch and Sayre,<sup>12</sup> the clinical picture resulting from innominate obstruction secondary to aortic dissection is characterized by reduced blood pressure and pulse volume in the homolateral upper extremity, in addition to the neurologic deficit produced by carotid involvement.

The occurrence of innominate artery occlusion without known underlying intrinsic disease of this vessel or neighboring vessels has not been previously described to our knowledge. Honig and his co-workers, in an angiocardio-graphic study of the innominate, do not report an instance of thrombosis.<sup>13</sup> A review of the diagnostic files at the Presbyterian Hospital over the past 24 years has failed to disclose a clinically diagnosed case of innominate obstruction. The

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following is a report of such a patient, recently observed, in whom angiocardio-graphic confirmation was obtained. So far as can be determined, this is the first case on record to be established roentgenographically.

#### CASE REPORT

A 40 year old single white woman was admitted to the Neurological Institute on November 3, 1952, with the chief complaint of weakness in the left arm and leg for 10 weeks. Of tangential interest in the past history were excessive alcoholic intake in the past three years, with an apparently adequate diet, and three previous breast operations for histologically demonstrated chronic cystic mastitis without signs of carcinoma. There was no knowledge of a venereal infection at any time. The systolic blood pressure was known to have been in the range of 190 mm. Hg for at least two years. The present illness began suddenly three weeks before her first visit to Vanderbilt Clinic. At the onset, she had gone to bed feeling perfectly well, but on trying to get out of bed the next morning had fallen to the floor. She did not become unconscious, but complained of numbness and inability to move her left arm and leg. There was no headache, neck or chest pain, and she noted no right-sided visual impairment. She and her family noted thick speech (not aphasia), and in the ensuing days a rather striking degree of emotional lability. She was admitted to another hospital where a diagnosis of "cerebro-vascular accident" was made, with the finding of left arm and left facial paresis. Brachial artery blood pressure (side not stated) was 95/70 mm. Hg. The patient left that hospital against advice, but was referred to this clinic when her private physician found an inequality in the brachial artery blood pressures, the right being 90/70, the left 190/100 mm. Hg. According to this doctor, earlier readings had shown the right arm blood pressure to be only 10 mm. Hg less than the left.

Initial clinic examination revealed a left hemiparesis, more marked in the arm than in the leg, with preponderance of the left deep tendon reflexes and a left Babinski sign. The reported blood pressure inequality was confirmed, and absent right radial and right common carotid artery pulsations were noticed. Pressure on the left common carotid failed to reduce blood flow through the retinal vessels on the right. It was felt that the patient's condition had stabilized following dissection of an aortic aneurysm, with compromise of blood flow through the innominate and its branches, and she was sent home for rest and physical therapy. She was seen six weeks later in the Neurology Clinic. There, she told of improvement to the point of ambulation and return of useful function of the left arm, only to wake one morning eight weeks after her first symptoms with recurrent loss of strength in the left extremities. Again, she noted no headache or chest pain, and there were no visual changes. The finding of increased left-sided weakness precipitated her admission in the tenth week of the illness.

General physical examination showed a pale, obese, left-handed woman in no acute distress, although easily moved to tears. Vital signs were normal except for the blood pressure, which was 160/110 mm. Hg in the left arm and 120/80 mm. Hg in the right. The eye grounds showed slight arteriolar narrowing, with normal optic discs bilaterally. The lungs were clear and the heart was normal. The liver edge was palpable four fingerbreadths below the right costal margin. No spider angiomas were seen. Neurologic examination again revealed a left hemiparesis, more marked in the arm than in the leg, the left hand being held in flexion. The gait was hemiparetic, with circumduction of the left lower extremity. Speech was dysarthric but there was no aphasia. Predominance of left deep tendon reflexes and a left Babinski sign with confirmatory pathologic toe responses were noted. Sensory examination was normal except for extinction phenomenon to pain stimulation

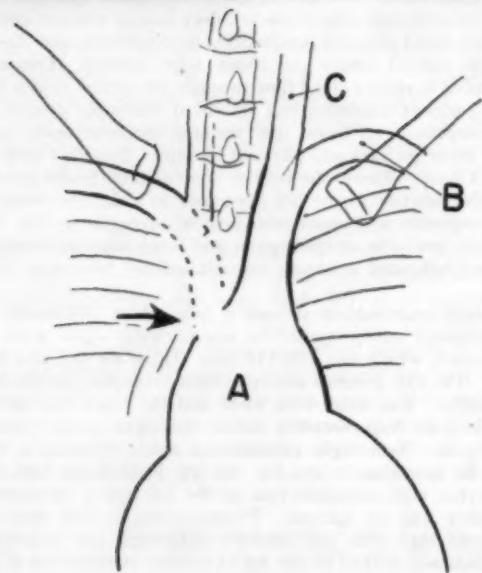
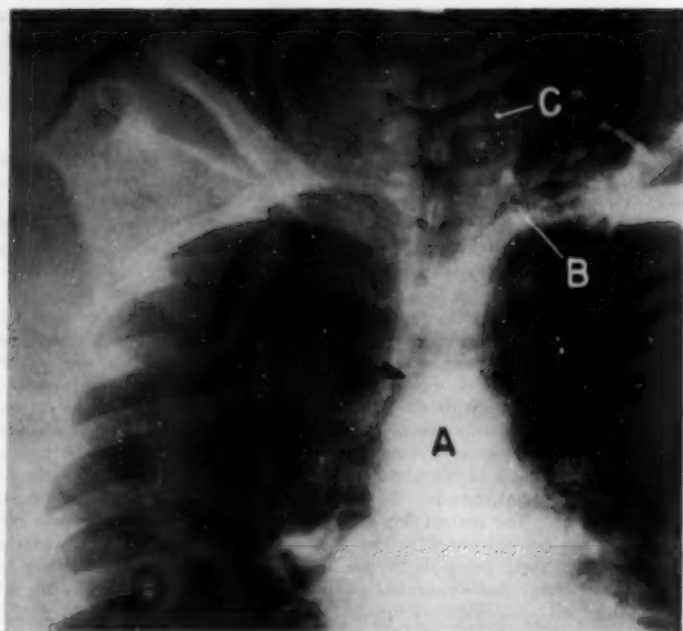


FIG. 1.

on the left, and left-sided astereognosis. The only abnormality in the cranial nerves was a mild left central facial paresis. Examination of the peripheral arteries showed an absent right and normal left common carotid pulsation; the right axillary and radial pulsations were markedly reduced in volume compared with the left, and lower extremity arterial pulsations were normal on both sides.

Laboratory examination was largely unrevealing. The red and white blood cell counts, erythrocyte sedimentation rate, urinalysis, fasting blood sugar and nonprotein nitrogen were all within normal limits. A blood serologic test for syphilis (Mazzini) was negative. The heart and lungs were normal by x-ray and fluoroscopy. There was no evidence of tortuosity or aneurysmal dilatation of the aorta or other great vessels, or of a mass impinging upon them. The electrocardiogram showed no abnormalities. Evaluation of liver function showed 33 per cent retention of bromsulphalein 30 minutes after dye injection, while the cephalin flocculation and thymol turbidity were negative and the serum alkaline phosphatase was normal.

Further study of the patient's neurologic status was carried out. Skull films were normal, showing the pineal body to be in the midline. Lumbar puncture produced a clear cerebrospinal fluid under normal pressure, containing 12 white cells per cubic millimeter without red cells, and 46 mg. per cent of total protein. The colloidal gold and Kolmer tests were negative. Electroencephalography demonstrated a "highly suggestive right temporal slow wave focus and . . . a depression of right occipital alpha activity." Visual fields suggested a left incomplete homonymous hemianopsia.

The impression was that the patient had suffered a partial occlusion of the innominate artery, leading to reduced blood flow through the right subclavian artery, with lowered blood pressure and pulse volume on that side, and to blockage of the right common carotid with right-sided encephalomalacia and resultant left-sided hemiparesis. In addition, it was felt that she might have Laennec's cirrhosis.

To establish more exactly the site of vascular occlusion, angiocardiology was performed, using two injections of 50 c.c. of 70 per cent Urokon into the left antecubital vein. Films were taken at two-second intervals by seriogram. On the anteroposterior projections, filling of the innominate artery and right common carotid artery was never seen. Figure 1, an anteroposterior view taken at four seconds, shows satisfactory opacification of the aorta, which is of normal width. The "double contour" typical of dissecting aortic aneurysm is not seen. The innominate artery, easily seen in the normal (its usual width at its midpoint averaging 10 mm.<sup>13</sup>), is not visualized. Normal filling of the left common carotid, left vertebral and left subclavian arteries is clearly made out. For comparison, figure 2 demonstrates innominate artery filling as it is seen in a subject without arterial disease. Figure 3, an anteroposterior view taken at six seconds, again shows failure of the innominate and right common carotid arteries to fill. (There was no filling of these vessels in subsequent serial films.) The left subclavian and its branches, and the left common carotid, are still visible. The right subclavian and its first branch, the right vertebral, are dimly perceptible. In the right posterior oblique view the innominate artery was again not seen. However, in this projection the right common carotid did fill, although less completely and one second later than the left common carotid. Figure 4, a right posterior oblique view taken at nine seconds, demonstrates good filling of the aorta, left subclavian and left common carotid arteries. Comparable filling of the right subclavian is seen, while the right common carotid appears narrower, a finding interpreted as "less complete" filling as compared with the left.

FIG. 1. Patient's angiocardigram. Anteroposterior projection, 4 seconds after dye injection. Note normal aortic width (A), filling of the left subclavian (B), and left common carotid (C). The innominate and its branches are not visualized. The arrow indicates the position normally occupied by the innominate, which is outlined by dotted lines in the diagram.

The radiographic impression was partial obstruction of the innominate artery due to uncertain cause, with thrombosis the most likely possibility.

The angiocardigram seemed to confirm the clinical impression, and because of the possible danger to already damaged blood vessels,<sup>6</sup> and the negligible therapeutic possibilities in a situation of this chronicity, common carotid angiography was not performed.

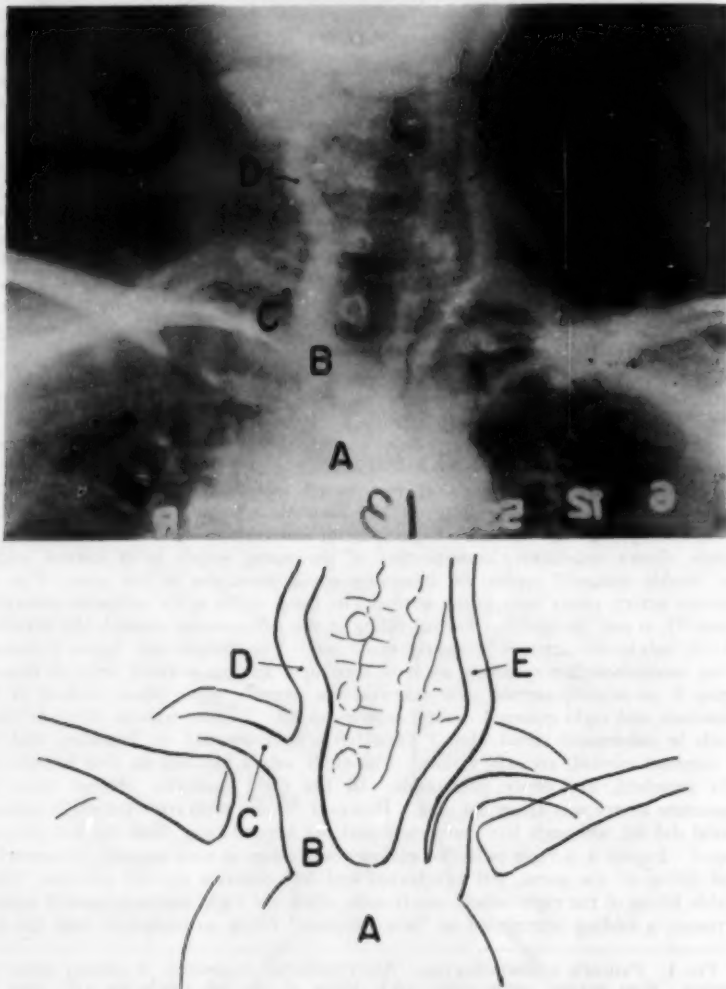


FIG. 2. Normal angiocardigram showing conspicuous filling of the innominate artery and its branches. (A) aorta, (B) innominate, (C) right subclavian, (D) right common carotid, and (E) left common carotid. The diagram is appended for clarity.



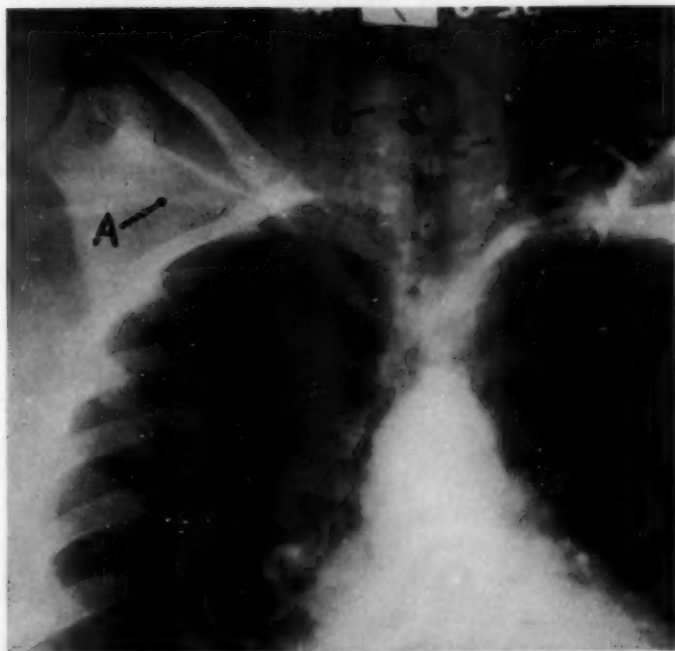


FIG. 3. Patient's angiocardiogram, anteroposterior projection, 6 seconds after dye injection. Nonfilling of the innominate and right common carotid arteries is again noted, but the right subclavian (A) and its branch, the right vertebral (B), are seen. The left common carotid (C) and the left subclavian with its branches are still visible.

The hospital course was marked by very slight improvement in function of the hemiparetic extremities. Gait was better, but spastic contractures of the fingers of the left hand remained. Speech remained slowed, and the patient was still emotionally labile, crying over trivia at the time of discharge on December 6, 1952. Seen in the Clinic five months after leaving the hospital, she reported some improvement in speech and gait, but the examiner noted little if any objective neurologic change for the better. The findings in the peripheral arteries remained the same.

#### DISCUSSION

The fact that contralateral hemiplegia or hemiparesis often follows obstruction of a carotid artery may be taken as evidence that cerebral circulation to the affected side cannot always be adequately maintained through the circle of Willis.<sup>1, 2, 8</sup> The degree of functional impairment depends in part on the prior state of the cerebral blood vessels. In this connection, the occurrence of clinical encephalomalacia in a 40 year old woman is perhaps less surprising, in view of her chronic hypertensive vascular disease, with its statistical predisposition to arteriosclerotic change. That other factors play a part is evident from the 5 to 20 per cent incidence of contralateral neurologic signs reportedly follow-

ing surgical ligation of the innominate even in young, nonhypertensive subjects.<sup>14</sup> After ligation of the common carotid artery, Galdston et al. estimate a 10 to 30 per cent incidence of cerebral damage as evidenced by contralateral neurologic deficit.<sup>2</sup>

It is of interest that the clinical course of carotid artery occlusion is extremely variable. It may be explosive, slowly progressive, recurrent or even silent, or symptoms may be restricted to visual changes with findings of homolateral



FIG. 4. Patient's angiocardiogram, right posterior oblique projection, 9 seconds after injection of dye. Note aortic filling, nonfilling of the innominate (arrow again shows its normal position), with opacification of the right subclavian (A), and filling of the right common carotid (B), which appears to be narrower and less opaque than the left common carotid (C).

amaurosis and optic atrophy.<sup>8</sup> In this case the recurrent character of the symptoms, the lack of clinical right optic nerve involvement and the partial filling of the right common carotid seen on the oblique projections in the angiocardiographic study all seem to point toward an incomplete rather than a total occlusion of the innominate artery.

The symptoms and signs of right hemispheric encephalomalacia in this case can be explained by the demonstrably reduced right common carotid artery blood flow (figure 4) resulting from this incomplete innominate obstruction. Contributory factors may also be "peripheral spasm" of cerebral vessels, as postu-

lated by Fisher,<sup>8</sup> or "forward embolism" from the site of thrombosis.<sup>4</sup> However, the pathogenesis of the primary lesion, partial occlusion of the innominate, is not definitely established. At least four possible underlying diseases appear to be ruled out. There is no radiographic suggestion of aneurysm or tortuosity of the innominate.<sup>13</sup> Trauma is excluded by history. Plain films and fluoroscopy of the thorax afford no evidence of an extrinsic mass pressing on upper mediastinal structures. And although about one fifth of patients with luetic aortitis have negative serologic tests, syphilis seems a remote possibility without a history of previous infection or radiographic signs of aortic or innominate aneurysm.

Dissecting aortic aneurysm with innominate and carotid involvement, as suspected on the patient's first clinic visit, might explain the findings. Preexisting hypertension, present here, is a commonly associated feature.<sup>10, 12</sup> Neurologic complications are not uncommonly found,<sup>10, 11, 12</sup> and when hemiparesis appears it is attributable to ischemic necrosis of the brain.<sup>11</sup> However, the fact that there was no chest pain, reported to occur in two thirds or more of cases,<sup>10, 12</sup> and the lack of evidence of aortic widening by x-ray, make this diagnosis less likely. While only 10 of 20 cases in Levinson's group examined by means of routine chest films showed widening of the aorta,<sup>10</sup> the absence in this case of angiocardigraphic evidence of narrowed or double aortic lumen would seem to weigh rather heavily against aortic dissection.

One is left with the impression that the findings in this patient represent a spontaneous thrombosis partially occluding the lumen of the innominate artery. The most likely basis for thrombosis is statistically an atherosclerotic plaque in the intima of the vessel. This can be neither proved nor excluded on clinical grounds.

Whatever the exact anatomic basis for the innominate artery occlusion, the important point to be made is that the picture of an "ordinary" cerebral vascular accident is here produced by an unusual vascular lesion. As Hunt pointed out nearly 30 years ago, the symptoms and signs of extracranial arterial lesions are "perfectly well known, but . . . we instinctively associate them with intracranial vascular disease."<sup>1</sup> Though carotid artery thrombosis is the more frequent cause of extracranial vascular involvement, occlusion of more proximal blood vessels such as the innominate may occasionally give rise to a similar picture. The distinguishing feature of innominate involvement is the occurrence of decreased pulse volume and lowered blood pressure in the homolateral upper extremity, in addition to loss of homolateral common carotid pulsation and contralateral hemiparesis.

Routine examination of extracranial arteries in cases of cerebral vascular insufficiency may thus uncover local or generalized vascular disease, giving new implications to lesions thought at first to be solely intracranial.

#### SUMMARY

1. A case is described of spontaneous partial occlusion of the innominate artery with compromise of the circulation through the right subclavian and right common carotid arteries. The clinical features are reduced brachial artery blood pressure and reduced radial artery pulse volume on the affected side, with

homolateral absence of common carotid artery pulsation and contralateral hemiparesis. The angiocardigraphic picture of a nonfilling innominate artery is presented.

2. Possible mechanisms of production of such a lesion are discussed.

3. The importance of examining extracranial arteries in all cases of cerebral vascular damage is emphasized.

4. The usefulness of special radiographic technics in demonstrating extracranial vascular occlusion is shown.

#### ACKNOWLEDGMENT

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## EDITORIAL

### STEADY WEIGHT

BECAUSE of clinical interest in overweight and underweight patients and in the factors operative in producing such conditions, physicians are apt to devote little attention to the tantalizing problem of how it comes to pass that many normal adults unconsciously regulate their food intake so that they remain within a few pounds of the same weight often for 10 or more years at a stretch.

Those persons best exhibiting this remarkable example of homeostasis are usually adults in the middle third of the normal life term. They are also apt to be settled people whose habitat has not altered climatically, whose job has been stable, whose daily schedule has not varied and who have been able to bear the stresses of their personal lives without emotional decompensation.

In such individuals the steady weight they exhibit may be within the so-called "ideal"<sup>1</sup> range for their height and bodily frame, or it may be sufficiently above this level to deserve the term obesity, or below the ideal to the point of marked thinness. The significant point is the existence of an automatic regulation which for long periods can effect so exact a matching of energy intake to energy output that there is neither increased storage of reserve energy with weight increase nor depletion of existing stores with loss of weight.

Granted an adequate food supply, the food intake of the normal man living on a regular schedule is governed by a desire to eat which recurs usually three times a day and which we term appetite; and by a sense of having had enough food, of being "satiated." Appetite and satiation evidently are the conscious elements of that delicate mechanism that, when operating optimally, so perfectly maintains the body in energy equilibrium.

Medical speculations as to the nature of hunger and appetite date back for centuries. It was assumed early (Haller, Weber) that fasting produced a change in the tissues that stimulated afferent nerves, so giving rise to the sensation of hunger. Magendie suggested the existence of a hunger center in the brain which was sensitive to a starvation state of the blood. Roux and others held to the belief that afferent nervous impulses arising from the viscera, and in particular the stomach, played a part in the production of hunger and appetite.

The relation of hunger pangs to strong peristaltic contractions of the stomach was demonstrated by Cannon and Washburn<sup>2</sup> and studied more fully by Carlson.<sup>3</sup> The latter tied in the older idea of the influence of a

<sup>1</sup> Metropolitan Life Insurance Company: Ideal weights, Metropolitan Life Ins. Bull. 23: 6, 1943, and 24: 6, 1943.

<sup>2</sup> Cannon, W. B., and Washburn, A. S.: An explanation of hunger, Am. J. Physiol. 29: 441-454, 1912.

<sup>3</sup> Carlson, A. J.: Control of hunger in health and disease, 2nd impression, 1916, University of Chicago Press, Chicago, Ill.

hunger state of the blood by postulating that a fasting hypoglycemia might be the cause of the gastric contractions. The relation of hunger pangs to gastric contractions is accepted, but hunger in the sense of a disagreeably urgent craving for food obviously plays no part in the finer adjustment of food intake to energy needs which is under discussion. Hunger is, as it were, the signal of an emergency state with an increasingly dominant desire for food which ultimately may override all civilized conventions.

Appetite is a term that covers those relatively pleasurable sensations occurring both in anticipation of eating and in a diminishing manner during the consuming of a meal. It is a less hardy and less dominant sensation than hunger. Appetite may be "lost" because of worry or grief; it may be "killed" by a nauseous odor; it may be "whetted" by good company, or by sensuous delight in the taste or texture of food. But though there are many psychic depressants and stimulants of appetite, it is evident that such irregular and occasional influences, while they may affect adversely the maintenance of balance between energy intake and output, must stand quite apart and separate from the unconscious mechanism which, when left to itself, can maintain that balance so exactly.

Relatively recently, physiological experimentation in lower animals has helped to throw some new light on the nature of the regulation of food intake. It is of interest that both the "hunger center" in the brain and the "starvation state" of the blood postulated by earlier physiologists have found support in the results of these later investigations.

Hetherington and Ranson<sup>4</sup> in 1940 published work which showed that bilateral destruction of parts of the medioventral nuclei of the hypothalamus in the rat leads to obesity. This hypothalamic type of obesity is due to overeating, the food intake sometimes being as much as three times that ingested by the average normal animal. The question naturally arose whether this striking increase in food intake is due to an increase above normal of appetite or whether there was a decreased awareness of satiation. Miller, Bailey and Stevenson<sup>5</sup> found that rats with hypothalamic hyperphagia, if obliged to "work" to obtain their food, actually ate less than normal rats. They concluded that the cause of the overeating when food was made freely available was a failure in development of the normal feeling of satiation.

This distinction between increased appetite and decreased satiation as possible causes for overeating and consequent obesity received striking confirmation through the investigations of Anand and Brobeck.<sup>6</sup> Bilateral destruction of minute areas in the hypothalamus situated well lateral of the medioventral nuclei in both rats and cats was found to lead to complete aphagia. Though postoperatively the rats appeared quite normal in other

<sup>4</sup> Hetherington, A. W., and Ranson, S. W.: Hypothalamic lesions and adiposity in the rat, *Anat. Rec.* **78**: 149-172, 1940.

<sup>5</sup> Miller, N. E., Bailey, C. J., and Stevenson, J. A. F.: Decreased "hunger" but increased food intake resulting from hypothalamic lesions, *Science* **112**: 256-259, 1950.

<sup>6</sup> Anand, B. K., and Brobeck, J. R.: Localization of "feeding center" in hypothalamus of rat, *Yale J. Biol. and Med.* **24**: 141, 1951.



respects, they rejected all food placed in their cages and died of starvation. Similar results were obtained in cats. Anand found that a unilateral destructive lesion did not cause anorexia. In animals first rendered hyperphagic by bilateral destruction of the medial centers, later destruction of the lateral centers converted the overeating into complete aphagia. The natural deduction from these experiments is that the lateral centers are concerned with food intake and that their operation has some correspondence to the sensation of appetite, whilst the medial centers exert an inhibitory influence on eating paralleled in consciousness, perhaps, by the sense of satiation.

The proof that, in certain mammals at least, definite control centers exist whose proper integration could readily explain the automatically achieved balance between energy intake and output is an important enlargement of our knowledge of bodily homeostasis.

The question poses itself immediately, however, as to how these centers are governed so as to adjust the caloric intake to the energy output. It may be said at once that no complete answer to this question has as yet been found.

It appears evident that the efficient functioning of the two centers must comprise two separate classes of activities. The centers must receive some type of signal indicative of bodily nutritional needs, or of the absence of such needs; and in the second place, as a result of the reception of such signals, there must emanate from the centers other signals which reach the level of consciousness and result in the voluntary acts of feeding or discontinuance of feeding.

A considerable literature<sup>7</sup> has developed concerning experimental hypothalamic obesity. Several theories have been put forward as to how the hypothalamic centers are made aware of the status of the body as to the need for food intake to balance energy output. On the other hand, very little has been published, in the way even of conjecture, as to how the lateral and medial centers function so as to lead to the conscious acts of eating or discontinuance of eating.

One theory (Brobeck<sup>8,9</sup>) attempts to explain the cessation of feeding on the basis of the increase in total heat production arising from the assimilation of food. The specific dynamic action of the several types of foodstuff has long been known to account for increased heat production, and it has likewise been known that, in association with such heat production, mechanisms for increased heat loss, such as vasodilatation, go into action. Booth and Strang,<sup>10</sup> as far back as 1936, observed elevations in skin tem-

<sup>7</sup> Mayer, J.: Genetic, traumatic and environmental factors in the etiology of obesity, *Physiol. Rev.* 33: 472-508 (Oct.) 1953.

<sup>8</sup> Brobeck, J. R.: Food intake as a mechanism of temperature regulation, *Yale. J. Biol. and Med.* 20: 545-552, 1948.

<sup>9</sup> Brobeck, J. R.: Physiology of appetite, in *Overeating, overweight and obesity*, Proceedings of the Nutrition Symposium held at the Harvard School of Public Health, Boston, Massachusetts, October 29, 1952, 1953, The National Vitamin Foundation, Incorporated, New York.

<sup>10</sup> Booth, G., and Strang, J. M.: Changes in temperature of the skin following the ingestion of food, *Arch. Int. Med.* 57: 533-543, 1936.

perature following feeding, and correlated this rise with the onset of satiety. Temperature-sensitive cells in the hypothalamic centers might be thrown into action through the alterations in blood temperature associated with the specific dynamic action of foods, or the decreased metabolism of the fasting state. Such an explanation, however, meets with certain difficulties. It is hard to make it accord with the voracious appetite seen in the acute diabetic. Likewise, it appears to run contrary to the fact that thyroid extract, a hyperthermic agent, increases food intake. Mayer and Greenberg<sup>11</sup> have found that, in intact animals, short-term deprivation of food led to an increase rather than a decrease of central temperature.

Very extensive experimental work, using rats, mice, dogs and human subjects, has led Mayer and his associates to postulate a "glucostatic mechanism" of regulation of food intake. In a recent excellent review<sup>7</sup> of various factors in the etiology of obesity, Mayer discusses this theory in some detail, and furnishes references to the principal publications concerning it. Only a brief summary of the main points can be furnished here. The dependence of the central nervous system on a continued supply of glucose in the blood makes it a priori reasonable that in the brain there should be centers sensitive to the fluctuations in blood sugar levels. The glucostatic theory postulates that the lateral feeding centers and the medial satiety or inhibiting centers contain such glucose-sensitive cells, or gluco-receptors, as they have been termed. It has been found that measures which led to temporary increase in blood sugar levels corresponded to decreases in food intake, and vice versa. The most striking example of this relationship was obtained by the use of alloxan-treated hypophysectomized rats. Such animals lack the mechanisms for rapid reduction of blood sugar levels, and hence can be maintained in a hyperglycemic state over long periods of time. It was found that two daily glucose injections in such rats would reduce their food intake by one-half; while three such injections daily, which resulted in continued hyperglycemia, caused the death of these animals from starvation in spite of the availability of food in their cages.

The apparent contradiction of the theory afforded by the ravenous appetite of the acute diabetic, whose blood sugar is constantly high, may be explainable if one assumes that, to influence the gluco-receptor cells, glucose has to pass through the cell membrane into the intracellular structure. Where utilization of glucose is normal, the intracellular products of glycolysis will be in close correspondence to the blood sugar level. In the diabetic state, however, the block in the utilization of glucose may lead to a marked disparity between the two.

Not all those who have studied the carbohydrate metabolism of animals exhibiting hypothalamic obesity have obtained results which accord with the glucostatic theory of food intake control. Mayer has expressed the opinion that the majority at least of such discrepancies would disappear if

<sup>11</sup> Mayer, J., and Greenberg, R. M.: Hyperthermia in hypothalamic hyperplasia, *Am. J. Physiol.* 173: 523, 1953.

investigations were confined to comparable phases of the postoperative course in the experimental animals. The results as to blood sugar levels immediately postoperative are not readily comparable with those occurring later, when the first extreme hyperphagia has been replaced by a more moderate though still excessive food intake. It has been found that in general, following operations, there is a period first of rapid and then of more gradual weight gain. This has been called the stage of "active obesity." In time, a stage of weight stabilization ("static obesity") is reached. During the stage of active obesity Mayer and co-workers observed a lowering of nonfasted blood sugar levels which correlated well with the grade of hyperphagia. In the static phase of obesity in the experimental animal, carbohydrate tolerance proved to be normal or decreased.

Beaudoin et al.<sup>12</sup> made an interesting application to humans of this concept of the active and static phases of obesity. Two groups of obese women were studied. One had been selected because of their history of recent continuing weight gain to represent "active obesity"; whereas the other, composed of women who had been obese for many years and had maintained the same level of weight for a long time, were taken to represent instances of "static obesity." The six women of the actively obese group displayed definitely increased tolerance both to glucose and to meal carbohydrates, as compared to their control group. Their blood sugars would be falling at the end of 30 to 45 minutes after the test meal, while the values for the blood glucose of the six subjects with static obesity still were rising at the one hour mark.

There is, then, suggestive evidence that the glucostatic mechanism may indeed account for the ability of the hypothalamic centers to balance energy intake against energy output. It should be recognized, however, that this is at best only a partial solution of an extremely complicated problem. The method by which these centers bring into consciousness specific sensations of appetite and satiety, and determine conscious acts—feeding and stopping of feeding—is quite unknown. It is evident, too, that the basic mechanism that attempts to quantitate our food intake in accordance with our true nutritional needs, and so maintains a condition of steady weight, is subject to be overridden by many psychological factors. It seems reasonable, however, to suppose that the active interest now being shown in the study of experimental hypothalamic obesity will continue to yield facts which broaden our comprehension of nutritional problems in the human.

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<sup>12</sup> Beaudoin, R., Van Itallie, T. B., and Mayer, J.: Carbohydrate metabolism in "active" and "static" human obesity, *J. Clin. Nutrition* 1: 91-99 (Jan.) 1953.

## REVIEWS

*Cardiovascular-Renal Disease in Diabetes Mellitus: A Clinical Study.* (Also published as Supplement 281 to Acta Medica Scandinavica, Volume 146.) By SVERRE AARSETH. 252 pages; 17 × 24.5 cm. (paper-bound). Printed by Bøhler & Larsen, Oslo, 1953.

This book presents the author's study over a recent three year period of 312 hospitalized diabetic subjects, the severity of whose illnesses was such that one-fourth died during hospitalization. By simple, readily available, clinical and laboratory technics he investigated their cardiovascular and renal status, correlated the results, and compared them with previously published data. The first two chapters present the examination protocol, the laboratory methods used, and the incidence and description of disorders unrelated to diabetes. Subsequent chapters are concerned with retinopathy and other ocular lesions, hypertension, diseases of the heart, arteriosclerosis, renal diseases, neuropathy and lipoid necrobiosis. In them the author provides a detailed panorama of what is actually going on clinically at the present time in a large diabetic population. It is his hope that this material will serve as a base for further, more fundamental studies.

P. F.

*Le Leptospirosi.* By MARIO AUSTONI, Professor, Institute of Medical Pathology, University of Padova. 715 pages; 17 × 24.5 cm.; paper-bound. Tipografia del Seminario, Padova, Italy. 1953. Price, 5,000 lira (\$8.00).

An extensive review of the present knowledge of leptospiral infections of man and animals is presented. Much of the material is based on the author's own clinical observations and illustrative cases from his experience are given in detail. Emphasis is on the epidemiology and clinical manifestations of the leptospiroses. The experimental aspects and bacteriology are well covered and several excellent and complete tables are used in these sections. The worker actively engaged in work with this group of diseases will find this book a most valuable reference.

M. J. S.

*Roentgen-Diagnostics* (Volume III, *Thorax*). First American Edition (Based on the Fifth German Edition.) By H. R. SCHINZ, W. E. BAENSCH, E. FRIEDL, and E. UEHLINGER. English translation arranged and edited by JAMES T. CASE, M.D., D.M.R.E. (Camb.), Professor of Radiology Emeritus, Northwestern University Medical School, Chicago. 1131 pages; 19.5 × 28 cm. (boxed), with 1084 illustrations. Grune and Stratton, New York. 1953. Price, \$45.00.

*Roentgen-Diagnostics* is the English edition of the *Lehrbuch der Roentgen Diagnostik*, which for many years has been an outstanding radiologic reference book. Volume III of this great work is devoted to a study of the chest, including both the pulmonary and vascular structures.

As in the two previous volumes, fundamentals of normal anatomy and its alteration in disease are stressed. Many minor details of normal radiographic anatomy, which are left undiscussed in most books, are clarified in this one.

All lesions of the pulmonary and vascular structures are thoroughly discussed from a clinical and physiological standpoint, but with the emphasis on the roentgen manifestations. The entities are magnificently and profusely illustrated with high quality roentgenograms, diagnostic sketches and charts.

This treatise is the most complete and authoritative piece of radiologic literature published in English. Through its exposition of fundamentals and its vast clinical

contents, it will be of immeasurable value, not only to the radiologists but to all medical specialists who make wide use of diagnostic roentgenography.

J. M. D.

*Diagnosis of Acute Abdominal Pain.* By WILLIAM REQUARTH, M.D., Clinical Assistant Professor of Surgery, University of Illinois College of Medicine; foreword by WARREN H. COLE, M.D. 243 pages; 14 × 21 cm. The Year Book Publishers, Inc., Chicago. 1953. Price, \$5.00.

The word "abdomen" is of Latin derivation meaning "from, to hide." Certainly the author has tried, in a concise manner, to bring from hiding lesions responsible for producing acute abdominal pain. Notable is the manner in which large subjects, e.g. acute intestinal obstruction, are summarized with all important signs, symptoms and examinations considered and tabulated. Justifiably, the value of minute and chronologic history taking is reiterated. The author classifies conditions which need immediate surgery, conditions in which surgery may be delayed and conditions in which surgery is contraindicated. He stresses clinical judgment which, of course, means experience. Such a book is always timely and should be valuable to the students, house officers or physicians who must repeatedly study and repeatedly apply the teachings.

H. C. H.

*Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels.* 5th Ed. By the Criteria Committee of the New York Heart Association, Inc., Harold E. B. Pardee, M.D., Chairman. 359 pages; 14 × 22.5 cm. New York Heart Association, Inc., New York. 1953. Price, \$4.95.

The present edition of this standard reference has increased value over earlier ones in that a section on diseases of the peripheral vessels has been included. In addition, there are chapters on Nomenclature for Cardiac Diagnosis, Criteria for Cardiac Diagnosis, Guide to Roentgenological Diagnosis, Criteria for Electrocardiographic Diagnosis, and Criteria for the Pathological Diagnosis of Diseases of the Heart and Great Vessels. Several new illustrations have been included and many of the sections have been completely rewritten. The illustrations are clearly presented and the text is well edited.

This volume is a valuable asset to any internist. It is an extremely useful reference volume and deserves a prominent place on the shelf of anyone interested in cardiology.

L. S.

*The Ballistocardiogram: A Dynamic Record of the Heart Beat.* Publication 143, American Lecture Series. By JOHN R. BRAUNSTEIN, M.D., Ph.D., Associate Professor of Biophysics and Assistant Professor of Medicine, University of Cincinnati, Cincinnati, Ohio. 84 pages; 14.5 × 22.5 cm. (leather-bound). Charles C. Thomas, Springfield, Illinois. 1953. Price, \$3.00.

This monograph on ballistocardiography includes two lectures delivered by the author in the Spring of 1951. It is an attempt . . . "to look at its remote and recent ancestors, its present condition, and hazard a guess or two as to the direction it will take in the future."

There are chapters devoted to history, instruments, the abnormal ballistocardiogram, cardiac output, clinical significance of the abnormal pattern and abnormal output, and the vectorballistocardiogram. Unfortunately, the text is brief without being clear; many illustrations are inadequately labelled; and the explanations are



often confusing. Insufficient emphasis is placed upon the influence of age and instruments on the registration of the ballistocardiogram. The most recently quoted reference in this rapidly developing controversial field is 1951. This monograph is not an important contribution to the field of ballistocardiography.

L. S.

*Practical Essays on Medical Education and the Medical Profession in the United States.* By DANIEL DRAKE, M.D. (1785-1852). 104 pages; 13.5 × 22.5 cm. Roff and Young, Cincinnati, Ohio. 1832. Reprinted by the Johns Hopkins Press, Baltimore, Md. 1952. Price, \$2.50.

This work is one of over 3000 items from the pen of one of America's great pioneer physicians. This reprint volume has an introduction by David A. Tucker, Jr., and was published one hundred years after Daniel Drake's death.

Persons concerned with medical education today could read with profit this series of essays among which are: Selection and Preparatory Education of Pupils; Medical Colleges; Studies, Duties and Interests of Young Physicians; and Causes of Error in the Medical and Physical Sciences. One cannot read these essays without being impressed by the author's philosophy, vocabulary and prose, and these are the more amazing considering that he was largely self-educated. In many instances he was greatly ahead of his time; he advocated four years in the study of medicine after preliminary education; advised the passage of laws governing medicine and pharmacy; outlined factors favorable to the establishment of medical colleges; and proposed a sensible code of ethics for the guidance of physicians practicing in the same locality.

The book is as fresh and stimulating as if written for present day readers to the following groups of whom it is warmly recommended: premedical students, medical students and physicians, especially those just starting into practice and those responsible in any way for some phase of medical education.

J. E. S.

*The Young Delinquent in His Social Setting: A Glasgow Study.* By T. FERGUSON, Professor of Public Health and Social Medicine, University of Glasgow. 158 pages; 14 × 22.5 cm. Oxford University Press, New York. 1952. Price, \$2.50.

The author, Professor of Public Health and Social Medicine at the University of Glasgow, in the course of another study (*The Young Wage-Earner*, 1951) of the work adjustment of boys who left school early, found that juvenile delinquency, judged by the court conviction rate, was a useful yardstick to measure adjustment.

The present study, growing out of the earlier one, attempts to discover what factors correlate most closely with delinquency. Three groups of boys were studied. The largest group consisted of 1,349 "ordinary" boys who left school at 14 years of age, the earliest permitted by law. The second group comprised 489 physically handicapped boys of about the same age. The third group was composed of 301 boys who had been in schools for mentally handicapped children and who had left school at 16 years of age.

The book is small, packed with tables, and the style is not very clear. The statistics are pretty simple, mostly in terms of percentages. The case illustrations are very brief, simple and not very revealing. There seems to be some confusion of concepts. Thus "poor scholastic attainment" is listed as an important factor contributing to delinquency, whereas it might more accurately be considered a symptom, occurring with delinquency, as part of a syndrome. The section on the response to court treatment is also somewhat disappointing. There was no description of what constituted probation in Glasgow, nor of what placement in institutions was like.



There was no mention of the use of psychological or psychiatric methods either in their studies or their treatment of individual boys.

The study of juvenile delinquency is an important topic and warrants a great deal of intensive research. Studies like the present volume, which developed secondarily out of other studies, can hardly be expected to provide the answers needed by those who are called upon to deal with this problem.

H. W. N.

#### BOOKS RECEIVED

Books received during March are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Acute Anuria: A Study Based on Renal Function Tests and Aspiration Biopsy of the Kidney.* By CLAUS BRUN. 215 pages; 24 × 16 cm. (paper-bound). 1954. Ejnar Munksgaard, Copenhagen. Price, D. kr. 30.00.

*Bacteriology for Medical Students and Practitioners.* 4th Ed. By A. D. GARDNER, D.M., F.R.C.S., F.R.C.P., Regius Professor of Medicine, Oxford Student of Christ Church, One Time Professor of Bacteriology and Fellow of University College, Oxford. 271 pages; 17.5 × 11 cm. 1953. Oxford University Press, New York. Price, \$3.00.

*The Billroth I Gastric Resection, With Particular Reference to the Surgery of Peptic Ulcer.* By HORACE G. MOORE, JR., M.D., Wilmington, North Carolina; formerly Instructor in Surgery, University of Washington School of Medicine, etc.; and HENRY N. HARKINS, M.D., Ph.D., F.A.C.S., Professor of Surgery and Executive Officer of the Department of Surgery, University of Washington School of Medicine, etc.; with a Foreword by DR. GÖSTA BOHMANSSON, Professor and Surgeon-in-Chief Emeritus, Central Hospital, Örebro, Sweden; and a Preface by DR. JOHN M. WAUGH, Head of a Section in the Division of Surgery, Mayo Clinic, etc. 175 pages; 27.5 × 20 cm. 1954. Little, Brown & Company, Boston. Price, \$7.50.

*Cardiovascular Surgery.* By GERALD H. PRATT, M.D., F.A.C.S., Associate Clinical Professor of Surgery, New York University College of Medicine, etc. 843 pages; 24 × 15.5 cm. 1954. Lea & Febiger, Philadelphia. Price, \$15.00.

*Current Therapy, 1954. Latest Approved Methods of Treatment for the Practicing Physician.* Edited by HOWARD F. CONN, M.D. Consulting Editors: M. EDWARD DAVIS, VINCENT J. DERBES, GARFIELD G. DUNCAN, HUGH J. JEWETT, WILLIAM J. KERR, PERRIN H. LONG, H. HOUSTON MERRITT, PAUL A. O'LEARY, WALTER L. PALMER, HOBART A. REIMANN, CYRUS C. STURGIS and ROBERT H. WILLIAMS. 898 pages; 27.5 × 20 cm. 1954. W. B. Saunders Company, Philadelphia. Price, \$11.00.

*The Dynamics of Virus and Rickettsial Infections: International Symposium Sponsored by the Henry Ford Hospital, Detroit, Michigan and held at the Hospital October 21, 22 and 23, 1953.* Editors: FRANK W. HARTMAN, M.D., FRANK L. HORSFALL, JR., M.D., and JOHN G. KIDD, M.D. 461 pages; 24 × 16 cm. 1954. The Blakiston Company, New York. Price, \$7.50.

*Einführung in die Vektorielle Deutung des EKG.* By DR. MED. HELMUT GILLMANN. 106 pages; 23.5 × 16 cm. (paper-bound). 1954. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price, Brosch. DM 19.-, geb. DM 21.-

*Embolia y Trombosis.* By TH. NAEGELI and P. MATIS. 162 pages; 23 × 16 cm. (paper-bound). 1954. Folia Clinica Internacional, Barcelona.

*Endogenous Endocrinotherapy, Including the Causal Cure of Cancer: Compendium.* 4th Ed. By DR. JULES SAMUELS, Surgeon-gynaecologist, Director of the Central Institute for the Samuels-Therapy, Amsterdam. 600 pages; 24 × 15.5 cm. 1954. N. V. Cyclocoop, Amsterdam. Price, 37 guilders.

*Financing Hospital Care in the United States: Recommendations of the Commission on Financing of Hospital Care.* 56 pages; 25 × 17 cm. (paper-bound). 1954. Commission on Financing of Hospital Care, Chicago. Price, \$1.00.

*Lectures on the Thyroid.* By J. H. MEANS, M.D., Jackson Professor of Clinical Medicine Emeritus, Harvard University, etc. 113 pages; 21.5 × 14.5 cm. 1954. Harvard University Press, Cambridge. Price, \$3.00.

*Leprosy: A Survey of Recent Legislation.* (Reprint from the International Digest of Health Legislation, 1954, 5, 3-36.) 35 pages; 24 × 16 cm. (paper-bound). 1954. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 25 cents.

*Manual of Clinical Mycology.* 2nd Ed. By NORMAN F. CONANT, Ph.D., Professor of Mycology and Associate Professor of Bacteriology, Duke University School of Medicine; DAVID TILLERSON SMITH, M.D., Professor of Bacteriology and Associate Professor of Medicine, Duke University School of Medicine; ROGER DENIO BAKER, M.D., Chief, Laboratory Service, Veterans Administration Hospital, Durham, N. C., etc.; JASPER LAMAR CALLAWAY, M.D., Professor of Dermatology and Syphilology, Duke University School of Medicine; and DONALD STOVER MARTIN, M.D., Chief, Bacteriology Section, Communicable Disease Center, Chamblee, Georgia. 456 pages; 20.5 × 14 cm. 1954. W. B. Saunders Company, Philadelphia. Price, \$6.50.

*Mayo Clinic Diet Manual.* 2nd Ed. By THE COMMITTEE ON DIETETICS OF THE MAYO CLINIC. 247 pages; 23.5 × 16 cm. (loose-leaf). 1954. W. B. Saunders Company, Philadelphia. Price, \$5.50.

*Methods in Medical Research.* Volume 6. Governing Board: IRVINE H. PAGE, Chairman; RENÉ J. DUBOS, C. N. H. LONG, CARL F. SCHMIDT, EUGENE A. STEAD and DAVID L. THOMSON. Editor-in-Chief: J. MURRAY STEELE. Some Methods of Studying Human Genetics: ANTONIO CIOCCO, Editor; Methods in Environmental Research: RAY G. DAGGS, Editor; Statistics in Medical Research: DONALD MAINLAND, Editor; Design and Construction of Metabolism Cages: ARNOLD LAZAROW, Editor. 271 pages; 22.5 × 14 cm. 1954. The Year Book Publishers, Inc., Chicago. Price, \$7.00.

*Mine Eyes Have Seen the Glory: The Story of a Virginia Lady, Mary Berkeley Minor Blackford, 1802-1896, Who Taught Her Sons to Hate Slavery and to Love the Union.* By L. MINOR BLACKFORD. 293 pages; 21.5 × 14 cm. 1954. Harvard University Press, Cambridge. Price, \$5.00.

*Pelvo-spondylitis Ossificans in the Male (Ankylosing Spondylitis, Morbus Bechterew-Marie-Strümpell) and Genito-urinary Infection: The Aetiological Significance of the Latter and the Nature of the Disease Based on a Study of 117 Male Patients.* By RAGNAR ROMANUS; translated by JOAN WHITEHOUSE. 368 pages; 24 × 17 cm. (paper-bound). 1953. Published as Supplement 280 to Volume 145 of *Acta Medica Scandinavica*. Price, 25 Swedish crowns.

- Phasenkontrast-Hämatologie.* By HANS FRANKE. 75 pages; 21 × 15 cm. (paper-bound). 1954. Georg Thieme Verlag, Stuttgart; available in U. S. A. and Canada from Intercontinental Medical Book Corporation, New York. Price, \$2.30.
- Plague: World Health Organization, Monograph Series No. 22.* By R. POLLITZER, M.D., formerly of the Division of Epidemiological and Health Statistical Services, World Health Organization. 698 pages; 25 × 16.5 cm. 1954. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, \$10.00 (cloth-bound) or \$9.00 (paper-bound).
- Practical Electrocardiography.* By HENRY J. L. MARRIOTT, M.D., Associate Professor of Medicine, University of Maryland, etc. 183 pages; 23.5 × 15.5 cm. 1954. The Williams & Wilkins Company, Baltimore. Price, \$5.00.
- Problems of Consciousness: Transactions of the Fourth Conference, March 29, 30 and 31, 1953, Princeton, N. J.* Edited by HAROLD A. ABRAMSON, M.D., Assistant Clinical Professor of Physiology, Columbia University College of Physicians and Surgeons, etc. 177 pages; 23.5 × 15.5 cm. 1954. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, \$3.25.
- Proceedings of the Annual Meeting, Council for High Blood Pressure Research, American Heart Association, Cleveland, Ohio, May 15-16, 1953. Volume II.* 94 pages; 23.5 × 15.5 cm. 1954. American Heart Association, New York. Price, \$2.00.
- Psychosomatic Case Book.* By ROY R. GRINKER, M.D., Director, Institute for Psychosomatic and Psychiatric Research and Training of the Michael Reese Hospital, etc.; and FRED P. ROBBINS, M.D., Associate Psychiatrist, Michael Reese Hospital, etc. 346 pages; 24 × 16 cm. 1954. The Blakiston Company, New York. Price, \$6.50.
- The Uncommon Heart Diseases.* By NATHANIEL E. REICH, M.D., F.A.C.P., F.C.C.P., Clinical Assistant Professor of Medicine, State University of New York, College of Medicine, etc. 516 pages; 24.5 × 16 cm. 1954. Charles C. Thomas, Publisher, Springfield, Illinois. Price, \$10.50.

## COLLEGE NEWS NOTES

### NEW LIFE MEMBERS

It is a pleasure for the College to announce that the following Fellows have become Life Members since the publication of the list in last month's issue of this journal:

Dr. Francis F. Harrison, Cooperstown, N. Y.  
Dr. Beeckman J. Delatour, South Worcester, N. Y.  
Dr. G. Gardiner Russell, West Hartford, Conn.  
Dr. Percy G. Hamlin, Canoga Park, Calif.  
Dr. Cassius H. Hofrichter, Seattle, Wash.  
Dr. Stuart Yntema, Saginaw, Mich.  
Dr. William G. Post, Jr., St. Petersburg, Fla.  
Dr. Samuel J. Weinberg, Los Angeles, Calif.  
Dr. Burdette J. Buck, West Hartford, Conn.  
Dr. Lloyd F. Craver, New York, N. Y.  
Dr. Frederick L. Landau, Jr., Bronxville, N. Y.  
Dr. Hugh Stalker, Grosse Pointe, Mich.  
Dr. B. Harrison Ragle, Boston, Mass.  
Dr. Alex. M. Burgess, Jr., Providence, R. I.  
Dr. M. B. Jarman, Hot Springs, Va.  
Dr. Howard F. Polley, Rochester, Minn.  
Dr. Jerald S. Falter, New York, N. Y.  
Dr. H. William Elghammer, Chicago, Ill.  
Dr. Truman G. Schnabel, Philadelphia, Pa.

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### A.C.P. RESEARCH FELLOWSHIPS

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1955-June 30, 1956. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work. The stipend will be from \$3,000 to \$3,500.

Application forms will be supplied on request to The American College of Physicians, 4200 Pine St., Philadelphia 4, Pa., and must be submitted in duplicate not later than October 1, 1954. Announcement of awards will be made November, 1954.

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### THE ELIZABETH ARCHBALD BOWES TRAVELING SCHOLARSHIP OF THE A.C.P.

Mrs. Margaret Bowes Murphy of Chicago has established with the American College of Physicians an additional Brower Traveling Scholarship to be known as "The Elizabeth Archbald Bowes Memorial Traveling Scholarship." Mrs. Murphy has established this Scholarship in memory of her mother and will support the Scholarship for a number of years. In all respects the same rules governing the Brower Traveling Scholarships will apply, except that this particular Scholarship

shall be restricted to Canadian candidates. The amount of the annual award will be \$400.00. The aim of the Scholarship is to provide an opportunity for a worthy young physician, preferably an Associate of the College, to spend a month, more or less, as a visiting fellow at some institution, or institutions, for observation and postgraduate study. The Committee on Fellowships and Awards of the College can readily facilitate opportunities at outstanding institutions where a month's observation, contact and study would be an exceptional inspiration and a practical source of training. Applications may be submitted by letter to the Executive Secretary of the College, 4200 Pine St., Philadelphia 4, Pa. The letter should designate the subject and type of work in which the candidate desires to engage; institution, or institutions, he would prefer visiting; the date that would be preferred by the applicant.

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#### NEW MASTERS

In keeping with the action of the Board of Regents on November 15, 1953, Masterships were conferred upon the following Fellows of the College at the recent Annual Convocation:

Dr. Walter L. Bierring, Des Moines, Iowa  
Dr. Robert A. Cooke, New York, N. Y.  
Dr. Egerton L. Crispin, Los Angeles, Calif.  
Dr. Hugh J. Morgan, Nashville, Tenn.

The late Dr. James S. McLester, F.A.C.P., Birmingham, Ala., was also elected a Master at the meeting of the Board of Regents last autumn.

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#### DR. THOMAS M. McMILLAN RECEIVES ALFRED STENGEL MEMORIAL AWARD

Dr. Thomas M. McMillan, F.A.C.P., Philadelphia, was granted the Alfred Stengel Memorial Award at the Annual Convocation of the College in Chicago, April 7. In presenting Dr. McMillan for the Diploma, Dr. Wallace M. Yater, F.A.C.P., Washington, D. C., said, "I have the honor to present Dr. Thomas M. McMillan, a recipient of the degree of Bachelor of Arts from Princeton University and the degree of Doctor of Medicine from the University of Pennsylvania. He was elected a Fellow of this College in 1933 and served as its acting Governor for Eastern Pennsylvania during the latter half of World War II, and as Governor since 1949. Since that time he has served also as Chairman of the Committee on Postgraduate Courses of the College and as such has greatly extended the program over a much wider field of subjects, with many new directors and with the participation of a large number of the medical schools and medical institutions of North America. Professionally, he has served and is serving in many important capacities. His professional attainments, his loyalty to the American College of Physicians and its members, his devotion to the principles and ideals of the College, and his participation in its activities have been outstanding."

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#### SIR W. RUSSELL BRAIN AND DR. ULF SVANTE VON EULER RECEIVE A.C.P. HONORARY FELLOWSHIPS

At the Annual Convocation of the American College of Physicians at Chicago, April 7, 1954, Sir Walter Russell Brain, London, England, and Dr. Ulf Svante von Euler, Stockholm, Sweden, were recipients of Honorary Fellowships.

Dr. Edward L. Bortz, F.A.C.P., Philadelphia, Pa., Chairman of the Committee on Masterships and Fellowships, in presenting the candidate, said, in part: "I have

the honor to present Sir Walter Russell Brain, Fellow and currently President of the Royal College of Physicians of London. A recognized authority in the field of neurology, he was knighted for his distinguished services in 1952. Son of a lawyer, he first studied law at Oxford, then served in the First World War, following which he returned to Oxford to read medicine, thereafter completing his medical training at London Hospital in 1922. He holds the honorary degree of Doctor of Laws, Wales, and has been nominated for the honorary degree of Doctor of Civil Law, Durham. Sir Russell is an Honorary Fellow of New College, Oxford, of the Royal College of Physicians of Ireland, of the Royal College of Physicians of Edinburgh, and of the Faculty of Radiologists, and last year was awarded the Heberden Medal. He is author of 'Recent Advances in Neurology and Neuropsychiatry,' a textbook, 'Diseases of the Nervous System,' and of a book on the philosophical aspects of neurology, 'Mind, Perception and Science.'

In presenting Dr. von Euler, Dr. Bortz said: "I have the honor to present Dr. Ulf Svante von Euler, Professor of Physiology since 1939 at the Medical Faculty of Stockholm, member of the Royal Academy of Science, member of the Nobel Committee for Physiology and Medicine of Stockholm, and corresponding or honorary member of academies and scientific societies in Barcelona, Buenos Aires and Santiago de Chile. Dr. von Euler conducted research studies as a Rockefeller Fellow in London, in Birmingham, in Ghent and in Buenos Aires. He has been the recipient of the Alvarenga Prize, Regnell's Prize and the Carl-Ludwig Medaille. He was awarded a Doctor's Honorary Degree by the University of Brazil. The author of many scientific contributions to the literature, Dr. von Euler is particularly known for his research on the neurohormone of the adrenergic nervous system (noradrenaline), concerning its formation, distribution and elimination from tissues and body fluids, and studies on the secretion of suprarenal medullary hormones, especially adrenaline, during various conditions, including stress."

#### A.C.P. POSTGRADUATE COURSES

All of the courses on the spring schedule of postgraduate courses have been concluded except the two following courses:

Course No. 7, INTERNAL MEDICINE: University of California Medical School, San Francisco; Dr. Stacy R. Mettier, F.A.C.P., Director.

Course No. 8, ISOTOPES IN CLINICAL MEDICINE: Ohio State University College of Medicine, Columbus; Dr. Charles A. Doan, F.A.C.P., Dr. William G. Myers, F.A.C.P., and Dr. Bruce K. Wiseman, F.A.C.P., Co-directors.

Both of these courses are being given June 14-18, the week preceding the A.M.A. annual meeting, and a limited number of registrants will still be accepted. Prompt application should be made to Mr. E. R. Loveland, Executive Secretary, 4200 Pine St., Philadelphia 4, Pa.

Following is the schedule of courses to be given during the coming autumn:

SELECTED PROBLEMS IN INTERNAL MEDICINE: University of Oklahoma School of Medicine, Oklahoma City; Dr. Wann Langston, F.A.C.P., Director; October 4-9.

BASIC CONCEPTS IN INTERNAL MEDICINE: Medical College of Virginia, Richmond; Dr. Charles M. Caravati, F.A.C.P., and Dr. Kinloch Nelson, F.A.C.P., Co-directors; October 11-15.

NEWER DEVELOPMENTS IN CARDIOVASCULAR DISEASES: Mount Sinai Hospital, New York; Dr. Arthur M. Master, F.A.C.P., and Dr. Charles K. Friedberg, F.A.C.P., Co-directors; October 11-15.



MEDICAL ASPECTS OF NEOPLASTIC DISEASES: Memorial Center for Cancer, New York; Dr. Cornelius P. Rhoads, F.A.C.P., and Dr. Rulon W. Rawson, F.A.C.P., Co-directors; October 18-22.

SELECTED SUBJECTS IN INTERNAL MEDICINE: University of Pittsburgh School of Medicine, Pittsburgh; Dr. Roy R. Snowden, F.A.C.P., Director, and Dr. Frank Gregg, F.A.C.P., Co-director; October 25-30.

INTERNAL MEDICINE: Beth Israel Hospital, Boston; Dr. Herrman L. Blumgart, F.A.C.P., Director; November 8-12.

GASTRO-ENTEROLOGY: University of Pennsylvania Graduate School of Medicine, Philadelphia; Dr. Henry L. Bockus, F.A.C.P., Director; November 15-19.

CARDIOLOGY: Michael Reese Hospital, Chicago; Dr. Louis N. Katz, F.A.C.P., Director (date to be announced).

PHYSIOLOGICAL BASIS OF INTERNAL MEDICINE: University of Pennsylvania Graduate School of Medicine, Philadelphia; Dr. Julius H. Comroe, Jr., F.A.C.P., Director (date to be announced).

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#### COMING EXAMINATIONS BY CERTIFYING BOARDS

*The American Board of Internal Medicine*, William A. Werrell, M.D., Executive Secretary-Treasurer, 1 W. Main St., Madison 3, Wis.

The following oral examinations are still to be given by the American Board of Internal Medicine:

Los Angeles—June 15-17, 1954,

New York City—Sept. 22-24, 1954.

May 1 was the closing date for the written examination of the Board, which will be held October 18, 1954.

*The American Board of Pediatrics*, John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Rd., Rosemont, Pa.

Oral Examinations: San Francisco, Calif.—June 25-27, 1954.

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#### A.C.P. 36TH ANNUAL SESSION

The 1955 Annual Session of the College will be held in Philadelphia, April 25-29, 1955. Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich., President of the College, is in charge of the program of General Sessions and Morning Lectures. Dr. Thomas M. Durant, F.A.C.P., Philadelphia, General Chairman, is in charge of arrangements, Panels, Clinics, Clinical-Pathological Conferences, and entertainment. General Headquarters will be at Convention Hall, and joint Hotel Headquarters will be at the Bellevue-Stratford and Benjamin Franklin Hotels.

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#### THE A.C.P. GROUP HEALTH AND ACCIDENT INSURANCE PLAN

The American College of Physicians Plan for Health and Accident Insurance has been re-opened for applications from those members who previously failed to subscribe. Only applications postmarked on or before June 15, 1954, will be accepted. Members who make application now will be able to participate in the benefits of this Plan regardless of their past history of sickness or accident, although the amount of coverage might be limited according to the regulations of the Plan. It is only necessary that a member be at work on a full-time basis on the day he sends in his application, and that he has been on such full-time basis for the preceding 30 days.

There is no assurance whatsoever that this opportunity will be repeated to old members of the College, although each new group elected will have an opportunity to subscribe within 60 days after election. Members who desire benefits to start at a future date may make a note of said date on the application and their policy will start at that time, provided they have been at work for 30 days on a full-time basis prior to that date.

Other Plans offered by other associations have been carefully analyzed. It is firmly believed that none offers as wide benefits at as low cost as does that of the College. If anyone is in doubt, he should not hesitate to ask the Association Service Office, 1500 Walnut St., Philadelphia 2, Pa., to furnish him with a comparison of their present Plan with that of the College.

Every member is urged strongly to study carefully the advantages offered and to get his application in to the Association Service Office without delay. This is the last opportunity to subscribe without submitting to physical selection.

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#### HAWAIIAN MEMBERS, A.C.P., MET FEBRUARY 18, 1954

Members of the College and guests, numbering 19, met at Lau Yee Chai's in Honolulu on February 18, 1954, with Governor Nils P. Larsen presiding. Candidates for membership were invited as guests. The agenda covered discussions of the Annual Meeting program of the College, postgraduate courses offered by the College, gifts to the Library, forthcoming medical meetings on the mainland and future meetings of the Hawaiian members of the College.

The Scientific Program was started by Dr. Henry Cooper who presented an interesting series, both experimental and clinical, of the effect of potassium on the EKG and the control of certain symptoms by the proper use of electrolytes. Dr. Morton Berk showed a series of cases on the effect of digitalis on the electrocardiograph. Dr. Fred Gilbert showed an assortment of interesting abnormal tracings, and Dr. Elmer Johnson presented a series of electrocardiographs to illustrate the value of the exercise test at certain times in clarifying certain problems.

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#### VIRGINIA REGIONAL MEETING

The regular annual Regional Meeting and scientific program of the Virginia Section of the American College of Physicians was held at Richmond, February 25, 1954, at the Richmond Academy of Medicine. Dr. John Powell Williams, Chairman of the Virginia Section, presided at the scientific meeting and the evening session. Members from the College from various parts of the state presented papers. At the close of the scientific session Dr. LeRoy H. Sloan, President of the College, Chicago, reviewed and discussed the papers. In the evening there was a cocktail hour and dinner at the Commonwealth Club for members of the Section and guests, who had the opportunity of hearing an address by President Sloan as well as one by Dr. Walter B. Martin, distinguished Fellow of the College and President-Elect of the American Medical Association. In attendance were 175 members and guests at the scientific session, and 108 members and 20 guests at the dinner.

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#### SECOND CONGRESS OF THE INTERNATIONAL DIABETES FEDERATION

The Second Congress of the International Diabetes Federation will be held in Cambridge, England, July 4-8, 1955. Sir Lionel Whitby, K.V.O., M.C., Master of Downing College, Cambridge, will be Honorary President. The Diabetic Association,

152 Harley St., London W.1., will act as host, and future publications in connection with the Congress will be issued by Mr. James G. L. Jackson, Executive Secretary-General of the Association.

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#### AUDIO-DIGEST FOUNDATION, CALIFORNIA MEDICAL ASSOCIATION

National distribution of tape recordings of the latest medical information has recently been undertaken by the California Medical Association through its newly-formed, non-profit subsidiary, Audio-Digest Foundation. Using tape recorded material, the Foundation makes available to doctors everywhere three "postgraduate services" designed to save their time while increasing the scope of their practice-useful knowledge.

The basic service is the weekly issuance of a one-hour tape for general practitioners. On it are recorded 20 to 30 abstracts of the best in current literature embracing all medical fields. Articles are screened by a board of medical editors headed by Edward C. Rosenow, Jr., M.D., F.A.C.P., Pasadena, Editor-in-Chief. As additional services, Audio-Digest offers semi-monthly digests in the fields of surgery, internal medicine, and obstetrics and gynecology, as well as lectures and panel discussions on one-hour reels for individual or group purchase.

Further details may be obtained from Mr. Jerry L. Pettis, Executive Director, Audio-Digest Foundation, 800 N. Glendale Ave., Glendale, Calif.

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#### DR. ALBERT H. HOLLAND, JR., APPOINTED MEDICAL DIRECTOR OF FDA

Dr. Albert H. Holland, Jr., former Medical Director of the Armour Laboratories, Chicago, has recently been appointed Medical Director of the Food and Drug Administration under the U. S. Department of Health, Education, and Welfare. As Director of the FDA Division of Medicine, Dr. Holland will be responsible for advising the agency on all medical questions involved in enforcement of the Federal Food, Drug, and Cosmetic Act. The Medical Division also assists in the development of medical evidence in court cases involving adulterated and misbranded products, and administers the new-drug provisions of the Act which require adequate scientific testing to establish the safety of all new drugs before they are placed on the market.

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#### THE OLDEST FELLOW OF THE COLLEGE

Dr. Henry F. Quackenbos, F.A.C.P., temporarily residing at 313 Wildemere Road, West Palm Beach, Florida, is 106 years of age, having been born in 1848. He is a charter Fellow of the American College of Physicians, having been elected in 1915. It has just recently been determined that he has been blind for many years, which accounts for the Executive Office of the College, because of no answers to inquiries during the past five years, presuming he had succumbed. Dr. Quackenbos spent most of his professional life in New York City. He holds the M.D. degree from the University of Virginia Department of Medicine (1891) and Bellevue Hospital Medical College (1893).

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#### A.C.P. OFFICIAL REPRESENTATIVES TO INTERNATIONAL POLIOMYELITIS CONFERENCE IN ROME

The President of the American College of Physicians has designated Drs. John R. Paul, F.A.C.P., and Dorothy M. Horstmann, F.A.C.P., both of New Haven, Conn.,

as official representatives of the College at the International Poliomyelitis Conference in Rome, Italy, September 6-10, 1954.

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#### THE GERALD B. WEBB MEMORIAL BUILDING DEDICATED

On March 12, 1954, at the Denison Auditorium of the University of Colorado, the Gerald B. Webb Memorial Building was officially dedicated. Dr. James J. Waring, M.A.C.P., President and Research Director of the Colorado Foundation for Research in Tuberculosis, was Chairman. The chief address was delivered by Dr. René J. Dubos, Philips Medalist of the American College of Physicians (1940), of the Rockefeller Institute for Medical Research, New York. Dr. Dubos' title was, "Tuberculosis, A Chronic Problem—For Research."

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#### THE CYRUS W. STRICKLER, SR., DOCTORS BUILDING

A new six-story building, named in honor of the late Dr. Cyrus W. Strickler, Sr., F.A.C.P., is scheduled to be completed in September in Atlanta. Dr. Strickler, who became a Fellow of the College in 1920, died July 23, 1953, and was Emeritus Professor of Clinical Medicine, Emory University School of Medicine, from which he graduated in 1897. Another memorial to Dr. Strickler, in the form of a scholarship in his name, is being planned by his friends in Atlanta. The scholarship will support a medical student at the Emory University School of Medicine. Donations to the Cyrus W. Strickler Memorial Scholarship Fund may be made through the Emory University Treasurer, Emory University, Ga.

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#### TENTH RHEUMATISM REVIEW

In the September and October, 1953, issues of the ANNALS OF INTERNAL MEDICINE was published the Review of the American and English Literature of Recent Years—Rheumatism and Arthritis. The demands for this Review were so great that the stock of the ANNALS OF INTERNAL MEDICINE for those months became exhausted. The American Rheumatism Association, Dr. W. H. Kammerer, Secretary-Treasurer, 33 E. 61st St., New York, N. Y., was authorized to reprint the Review in a single volume. That Association has a certain quantity of this Review available for purchase.

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#### NATIONAL INSTITUTE OF MENTAL HEALTH REVISES BOOKLET

A new edition of "Training and Research Opportunities under the National Mental Health Act" has recently been issued by the National Institute of Mental Health. The booklet has been revised to reflect policy changes with respect to traineeships (formerly called "stipends") and research fellowships.

In addition to traineeships available in psychiatry, psychiatric nursing, psychiatric social work and clinical psychology, a fifth area of study known as "public health mental health" has been added. These public health mental health traineeships are available to psychiatrists, clinical psychologists, psychiatric social workers, public health nurses with undergraduate degrees and public health officers.

Research fellowships are now awarded to postdoctorate investigators only. This program is designed to assist young scientists and physicians in obtaining training and experience in research techniques and methodology which may be applied to the problems of mental health and illness. These fellowships are available to qualified

research workers in many fields of science and medicine, such as biochemistry, neurophysiology, psychiatry, psychology, and sociology.

The new edition of the pamphlet also includes more detailed information on the policies and procedures of the research grant program of the National Institute of Mental Health.

Single copies of "Training and Research Opportunities under the National Mental Health Act" may be obtained free of charge from the National Institute of Mental Health, Bethesda 14, Md. If the applicant for a traineeship indicates the profession in which he is applying, a list of the universities and training centers awarding Public Health Service traineeships in that profession will be enclosed with the pamphlet.

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#### AMERICAN HEART ASSOCIATION MET IN CHICAGO

Under the Presidency of Dr. Robert L. King, F.A.C.P., Seattle, Wash., the American Heart Association held its Thirtieth Annual Meeting and Clinical Scientific Program in Chicago, March 29-April 4, 1954. Dr. E. Cowles Andrus, F.A.C.P., Baltimore, was the President-Elect. The Scientific Sessions were held on the last two days, April 3 and 4. A highlight of the last day's Session was the Lewis A. Conner Lecture, established in tribute to the first President and one of the founders of the American Heart Association, as well as a former Fellow of the American College of Physicians, which was delivered by Dr. Irvine H. Page, F.A.C.P., Director of Research of the Cleveland Clinic.

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Under the Presidency of Dr. W. Lindsay Miller, F.A.C.P., Gadsden, Ala., the annual meeting of the Southeastern Allergy Association was held March 25-27 in Atlanta. Among the speakers were Dr. Homer E. Prince, F.A.C.P., Houston, Tex., President-Elect of the American Academy of Allergy; Dr. John M. Sheldon, F.A.C.P., Ann Arbor, Mich., President of the American Academy of Allergy; and Dr. Oscar Swineford, Jr., F.A.C.P., Charlottesville, Va., past President of the American Academy of Allergy.

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Six members of the College were guest speakers at the annual scientific assembly of the American Academy of General Practice, held in Cleveland, March 22-25. Dr. William S. Middleton, M.A.C.P., Madison, Wis., discussed "Management of the Anemias," and Dr. Roscoe L. Pullen, F.A.C.P., Columbia, Mo., spoke on "Why Train for General Practice?" Dr. Howard A. Rusk, F.A.C.P., New York City, conducted a clinic on rehabilitation. Dr. Sol Katz, F.A.C.P., Washington, D.C., and Dr. Paul A. Bunn (Associate), Syracuse, N. Y., were the respective moderators for a Symposium on Tuberculosis and a Symposium on Antibiotics in Infectious Diseases. "The Family Doctor and Our Youth" was the topic of an address by Dr. Joseph F. Hughes, F.A.C.P., Philadelphia.

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Dr. Lemuel C. McGee, F.A.C.P., Wilmington, Del., has recently been elected to the American Medical Association's Council on Industrial Health. He succeeds Dr. Anthony J. Lanza, F.A.C.P., New York City, whose term has expired. Dr. Lanza, formerly Chairman of the Council, recently received an American Medical Association citation for distinguished service in the field of industrial health.

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Dr. Thomas Findley, F.A.C.P., New Orleans, former College Governor for Louisiana, will soon move to Augusta, Ga., where he will serve as Director of the

Georgia Heart Association Laboratory of Cardiovascular Research and will occupy the first chair of cardiovascular research at the Medical College of Georgia. In these new positions, Dr. Findley will be primarily devoted to research. He is presently Professor of Clinical Medicine at Tulane University of Louisiana School of Medicine and Head of the Medical Section at the Ochsner Clinic.

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Dr. Henry L. Ulrich, F.A.C.P., Minneapolis, was recently awarded a plaque by the Hennepin County Tuberculosis Association in recognition of his many years of work in the fight against tuberculosis.

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Wayne University College of Medicine, Wayne County Medical Society, and the Detroit Roentgen Ray and Radium Society gave a testimonial dinner for Dr. Lawrence Reynolds, F.A.C.P., Professor of Roentgenology at the College of Medicine, March 4. Dr. Reynolds also delivered the Hickey Memorial Lecture and was further honored by the establishment of a Lawrence Reynolds Radiological Niche in the new Wayne University Library. As part of the proceedings, Dr. Eugene P. Pendergrass, F.A.C.P., Philadelphia, participated in a discussion of "Vascular Radiography."

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Dr. Thomas M. McMillan, F.A.C.P., Philadelphia, Alfred Stengel Memorial Diplomate and College Governor for Eastern Pennsylvania, was honored by the Medical Board of Philadelphia General Hospital, March 22. An oil portrait of Dr. McMillan, retiring head of the hospital's heart clinic, was presented to the hospital by his colleagues.

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Dr. Joseph F. Siler, F.A.C.P., Colonel (Retired), M.C., U. S. A., and Dr. Walter A. Bloedorn, F.A.C.P., both of Washington, D. C., were recently reelected President and Secretary, respectively, of the Gorgas Memorial Institute of Tropical and Preventive Medicine.

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Dr. Paul D. Camp, F.A.C.P., Richmond, Va., was chosen President-Elect of the Tri-State Medical Association at the annual meeting in Charleston, S. C., Feb. 22-23.

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At the Sixth Annual Meeting of the Texas Rheumatism Association, Dr. Howard C. Coggeshall, F.A.C.P., Dallas, was elected First Vice President.

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Dr. Joseph Bank, F.A.C.P., Phoenix, Ariz., was recently chosen President-Elect of the Southwestern Medical Association.

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Dr. Edward D. Levy (Associate), Norfolk, has recently been elected Vice President of the Virginia Society for Pathology and Laboratory Medicine.

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Dr. Eugene H. Drake, F.A.C.P., Portland, Maine, was installed last month as President of the Council of New England State Medical Societies.

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Dr. William A. Read, Sr., F.A.C.P., Newport News, and Dr. James F. Conner (Associate), Kecoughtan, have recently been elected Vice President and Secretary-Treasurer, respectively, of the Virginia Diabetic Association.



Dr. Edwin A. Rasberry, Jr., (Associate), Wilson, N. C., was recently elected President of the Seaboard Medical Association of Virginia and North Carolina at the meeting held in Norfolk.

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Dr. R. Finley Gayle, Jr., F.A.C.P., Professor and Chairman of the Department of Psychiatry and Neurology at the Medical College of Virginia, was chosen President-Elect of the American Psychiatric Association at the annual meeting held in St. Louis, May 3-7.

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Dr. Tom D. Spies, F.A.C.P., Birmingham, was recently honored at a luncheon arranged by the Council of the Southern Medical Association. His citation read, "on completion of 25 years of unselfish service to humanity in the field of research, during which time he has given unsparingly of himself and his talents to study and devise better methods of recognition and treatment of disease." He has also been granted an honorary membership in the Cuban Society of Public Health. Dr. Spies is Director of the Nutrition Clinic at the Jefferson-Hillman Hospital in Birmingham and also is an Honorary Professor at the University of Havana.

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Dr. Emanuel Schwartz, F.A.C.P., Brooklyn, has recently been appointed a member of the Medical Practice Committee of the New York State Workmen's Compensation Board.

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Dr. Richard W. Vilter, F.A.C.P., Cincinnati, has recently been chosen by the World Health Organization to study the causes of anemia and nutritional deficiency diseases in Egypt for the United Nations. Dr. Vilter is Associate Professor of Medicine at the University of Cincinnati College of Medicine and is a member of the Committee on Dietary Allowances of the National Research Council.

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Dr. Walter C. Hausheer, F.A.C.P., Staten Island, N. Y., has recently joined the Medical Department of the Standard Oil Development Company.

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The Academy of Medicine of Cincinnati had as guest speakers in March, Dr. Charles K. Friedberg, F.A.C.P., New York City, Assistant Clinical Professor of Medicine at Columbia University College of Physicians and Surgeons, and Dr. Carl V. Moore, F.A.C.P., St. Louis, newly appointed Dean of Washington University School of Medicine. On March 2 Dr. Friedberg discussed "Drugs in the Treatment of Heart Disease," and on March 16 Dr. Moore delivered the Roger Morris Lecture, "New Concepts About Thrombocytopenic Purpura, Sensitivity to Platelets, and Platelet Types."

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Dr. Charles S. Davidson, F.A.C.P., Boston, and Dr. Frank H. Bethell, F.A.C.P., Ann Arbor, were among the out-of-state participants in a Symposium on Problems of Gerontology on March 2 in New York City. Their respective topics were "Protein Metabolism" and "Hemopoietic Factors." Dr. Henry A. Rafsky, F.A.C.P., New York City, discussed "Nutritional Problems of the Aged." The Symposium was jointly sponsored by the Johns Hopkins University School of Hygiene and Public Health and the National Vitamin Foundation.

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Dr. William Dock, F.A.C.P., Brooklyn, spoke on "Causes and Significance of Apical Localization of Tuberculosis" at a meeting of the St. Louis Medical Society, March 16. His lecture was sponsored by the St. Louis Society of Internal Medicine.

Dr. Leo H. Crip, F.A.C.P., Pittsburgh, gave a presentation on "Vascular Allergy" before the section on allergy of the Medical Society of the County of Kings and the Academy of Medicine of Brooklyn on March 18.

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Meeting for its Fifth Scientific Session on March 17 in Newark, the New Jersey Heart Association heard Dr. Emanuel Goldberger, F.A.C.P., New York City, discuss "Rotational Effects on the ECG. Stimulating Myocardial Infarction." Dr. J. Scott Butterworth, F.A.C.P., New York City, spoke on "Clinical Significance of Heart Sounds," and Drs. Benjamin M. Baker, Jr., F.A.C.P., and Martin L. Singewald, F.A.C.P., Baltimore, gave a presentation on "Modern Ballistocardiography." Dr. Samuel Bellet, F.A.C.P., Philadelphia, read a paper entitled "Ectopic Rhythms Secondary to Electrolyte Imbalance."

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Among those who have recently presented Kellogg Lectures at the George Washington University School of Medicine, Washington, D. C., were Drs. Thomas M. Durant, F.A.C.P., and Edward Weiss, F.A.C.P., Philadelphia. Their respective subjects on March 15 and March 17 were "Pathogenesis and Management of Coronary Atherosclerosis" and "Emotional Problems in Heart Disease."

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Under the sponsorship of the Albany Medical College, the Medical Society of the County of Albany, the Medical Society of the State of New York, and the New York State Department of Health, a cancer teaching day was held at the College, March 25. The program was presented by members of the Jefferson Medical College of Philadelphia and included Drs. Peter A. Herbut, F.A.C.P., and Louis H. Clerf, F.A.C.P., who were among those discussing "Cancer of the Bronchus." Dr. Franklin R. Miller (Associate) took part in the discussion of "Treatment of Leukemia."

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Dr. Samuel A. Levine, F.A.C.P., Boston, spoke on "Some Pitfalls in the Care of Cardiacs" on March 20 in Buffalo, N. Y., at the annual Clinical Day sponsored by the Alumni Association of the University of Buffalo School of Medicine. He also used this topic in delivering the annual George E. Fahr Lecture at the University of Minnesota Medical School, Minneapolis, March 23, where he participated in the continuation course in cardiovascular diseases, held March 22-24 at the Center for Continuation Study.

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Dr. Alvan L. Barach, F.A.C.P., New York City, was among the Stoneburner lecturers at the Medical College of Virginia, Richmond, March 24-26. His subjects were "Management of Pulmonary Emphysema" and "Mechanically Induced Bronchial Drainage in Respiratory Disease. The Principles and Techniques of Exsufflation with Negative Pressure." Dr. Edward S. Ray, F.A.C.P., Richmond, whose topic was "Pulmonary Osteoarthropathy," was among the local physicians on the program.

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Dr. Cornelius P. Rhoads, F.A.C.P., New York City, discussed "Advances in the Treatment of Neoplastic Diseases" at Tufts College Medical School, Boston, March 22. The lecture was sponsored by the Alpha Theta chapter of Phi Delta Epsilon at Tufts.

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Dr. Walter B. Martin, F.A.C.P., Norfolk, Va., who will be installed as President of the American Medical Association next month, will be the principal guest speaker at the 87th Annual Meeting of the West Virginia State Medical Association at White Sulphur Springs, Aug. 19-21. Dr. John S. LaDue, F.A.C.P., New York City, will

participate in a Symposium on Cancer and will deliver a paper entitled "Evaluation of the Operative Risk with Particular Attention to the Aged." Other guest speakers include Dr. George E. Burch, Jr., F.A.C.P., New Orleans, whose paper is entitled "Common Cardiac Conditions Amenable to Surgery," and Dr. Garfield G. Duncan, F.A.C.P., Philadelphia, who will discuss some aspect in the treatment of diabetes.

On Thursday afternoon, Aug. 20, the Third Annual Regional Meeting of the American College of Physicians will be held under the Governorship of Dr. Paul H. Revercomb, F.A.C.P., Charleston.

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The Fourth Middle East Medical Assembly was held at the Medical School of the American University in Beirut, Lebanon, on April 9-11, 1954, under the direction of Dr. Hobart A. Reimann, F.A.C.P. Distinguished speakers from the Arab States, England and the United States participated, including Sir Lionel Whitby, Brig. Gen. Sam Seeley, (MC), USA, Capt. A. R. Higgins, (MC), USN, F.A.C.P., Col. Robert J. Hoagland, (MC), USA, (Associate), Dr. Richard Taylor of the Rockefeller Foundation, Dr. Joseph McDonald and others. Subjects of importance to the region were discussed and illustrated in discussions and scientific exhibits.

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Dr. William Kaufman, (Associate), Bridgeport, Conn., will address the Third International Gerontological Congress, being held in London, England, July 19-23, on "Reversal of Some Phenomena of Aging by Vitamin Therapy" and "Psychosomatic Problems in Older People—The Fallacy of the Single Cause." Dr. Kaufman will also discuss "Management of the Transference Relationship in the Psychotherapy of Patients with Food Allergy" at the meeting of the International Congress for Psychotherapy to be held in Zurich, Switzerland.

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In addition to Dr. Charles A. Doan, F.A.C.P., Columbus, Ohio, Dr. Edgar R. Pund, F.A.C.P., Augusta, President of the Medical College of Georgia, and Dr. Carl Muschenheim, F.A.C.P., New York City, were among the distinguished guest speakers at the annual meeting of the Atlanta (Ga.) Graduate Medical Assembly, Feb. 22-24.

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Seven Fellows of the College were among the out-of-state speakers at the annual clinical conference of the Chicago Medical Society, held March 2-5 at the Palmer House. Speakers and their topics included Dr. J. Murray Kinsman, F.A.C.P., Louisville, "Medical Infections of the Kidney"; Dr. Francis D. Murphy, F.A.C.P., Milwaukee, "Types of Hypertension"; Dr. Harry L. Alexander, F.A.C.P., St. Louis, "Allergic Reactions to Drugs"; Dr. Marion B. Sulzberger, F.A.C.P., New York City, "Dermatological Disorders Commonly Encountered in General Practice"; Dr. Stewart G. Wolf, Jr., F.A.C.P., Oklahoma City, "Role of Stress in Peptic Ulcer"; Dr. Tom D. Spies, F.A.C.P., Birmingham, Ala., "Vitamins as Therapeutic Agents"; and Dr. Ferdinand C. Helwig, F.A.C.P., Kansas City, Mo., "Diagnosis and Management of Breast Tumors."

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Dr. Theodore G. Klumpp, F.A.C.P., New York City, President of Winthrop-Stearns, Inc., addressed a monthly dinner meeting of the Woman's Auxiliary of the Harrison County (W. Va.) Medical Society on Feb. 4 at the Stonewall Jackson Hotel in Clarksburg. His topic was "Geriatrics."

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Dr. Franklin D. Murphy, F.A.C.P., Lawrence, Chancellor of the University of Kansas, was the banquet speaker on March 25 at the 1954 National Health Forum, which convened in New York City, March 24-26.

Speakers and their topics at the 25th Annual Meeting of the Aero Medical Association, held in Washington, D. C., March 29-31, included Col. Don D. Flickinger, (MC), USAF, F.A.C.P., Baltimore, "Requirements for Crew Effectiveness in the B-52 Strategic Bomber," and Col. William R. Haas, (MC), USAF, (Associate), Washington, D. C., "The Use of Anti-Malarial Drugs in Flying Personnel." Capt. Leon D. Carson, (MC), USN, F.A.C.P., Washington, D. C., was one of the members of a panel on "The Aging Pilot."

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Under the Presidency of Dr. Arthur C. Curtis, F.A.C.P., Ann Arbor, the Fifteenth Annual Meeting of The Society for Investigative Dermatology, Inc., will be held in San Francisco, June 19-20, 1954. Dr. Curtis' Presidential address is entitled "The Chronicle of the Society for Investigative Dermatology," and he is also one of the contributors to the presentation on "Studies on Fungi Encountered in the Atmosphere. II. Production of Dermatitis in Guinea Pigs by Crude Ether-Soluble Extracts of *Alternaria*, *Hormodendrum*, *Penicillium* and *Aspergillus*." Dr. Walter C. Lobitz, Jr. F.A.C.P., Hanover, N. H., is one of the co-authors of "The Epidermal Eccrine Sweat Duct Unit," and Lt. Col. William N. Piper, (MC), USA, (Associate), Washington, D. C., is among the contributors to "Studies on the Effect of Ultraviolet Light on the S-H and S-S Groups in Human Keratin and Serum." Dr. John R. Haserick (Associate), Cleveland, is one of two co-authors of "The Kveim Test in Sarcoidosis: Investigation and Evaluation."

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Dr. Howard A. Rusk, F.A.C.P., New York City, delivered the James M. Anders Lecture at the College of Physicians of Philadelphia on March 3, his subject being "The Physician and the Changing World."

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Among the guest lecturers at the spring series of graduate lectures sponsored by the Department of Medicine, University of Virginia, Charlottesville, was Dr. William B. Castle, F.A.C.P., Boston, on March 1, whose title was "Some Immunologic Aspects of Disorders of the Blood."

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Dr. Seymour J. Gray, F.A.C.P., Boston, presented a paper on "Hormonal Influences in Peptic Ulcer Disease" at a meeting on March 8 of the New York Chapter of the American College of Gastroenterology. The meeting was held at the New York Academy of Medicine, New York City.

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Dr. Walter L. Palmer, F.A.C.P., Chicago, Dr. Max S. Allen, (Associate), Kansas City, Kans. and Dr. Howard A. Rusk, F.A.C.P., New York City, were among the guest speakers at the Second Lincoln-Lancaster Medical Conference, held March 11 at the Cornhusker Hotel, Lincoln, Nebr.

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Dr. E. Perry McCullagh, F.A.C.P., Cleveland, was one of four guest speakers at a combined meeting of the New York Heart Association, Inc., and the Clinical Society of the New York Diabetes Association, held March 9 in New York City. His subject was "Relation of Control of Diabetes Mellitus to Plasma Protein Patterns and the Development of Vascular Degeneration." At the same meeting, Dr. Harold Rifkin, F.A.C.P., New York City, discussed "Kimmelstiel-Wilson Syndrome and Its Clinical Variants."

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Sponsored by the Michigan State Medical Society, Wayne County Medical Society, Michigan Heart Association, American College of Surgeons, the medical schools of Wayne University and the University of Michigan, and related organiza-

tions, the annual Michigan Clinical Institute was held in Detroit, March 10-12. The R. S. Sykes Lecture, "Difficulties in Early Diagnosis of Lung Cancer," was delivered by Dr. Eugene P. Pendergrass, F.A.C.P., Philadelphia. Dr. John H. Warvel, Sr., F.A.C.P., Indianapolis, spoke on "Treatment of Diabetic Emergencies," and Dr. Frederick W. Niehaus, F.A.C.P., Omaha, discussed "Alcoholism and Cardiovascular Disease." Among the other speakers were Dr. George E. Wakerlin, F.A.C.P., Chicago, whose subject was "Pathogenesis and Treatment of Essential Hypertension," and Dr. Stanley F. Hampton (Associate), St. Louis, who used "Differential Diagnosis and Treatment of Extrinsic and Intrinsic Asthma" as his topic.

As part of the 1954 Industrial Health Conference, the Industrial Medical Association met in Chicago, April 26-30. Those presiding at various meetings included Dr. Robert C. Page, F.A.C.P., New York City, President-Elect of the Industrial Medical Association; Dr. Elston L. Belknap, Sr., F.A.C.P., Milwaukee, Dr. Norman Plummer, F.A.C.P., New York City, and Dr. Leo J. Wade, F.A.C.P., New York City. Dr. Plummer also participated in a discussion of "How the Industrial Physician Looks at the Causes and Cures of Absenteeism"; and Dr. Edward J. Stieglitz, F.A.C.P., Washington, D. C., discussed "Constructive Health—Management's Stake in Industrial Health Programs."

#### ELECTIONS TO MEMBERSHIP IN THE AMERICAN COLLEGE OF PHYSICIANS

At the Thirty-Fifth Annual Session, held in Chicago, Ill., April 5-9, the following candidates were elected to membership in the College (Fellows indicated in FULL CAPITALS; Associates, Lower Case):

ARTHUR SIMON ABRAMSON.....	New York, N. Y. (V.A.)
MELVIN LOUIS AFREMOW.....	Chicago, Ill.
John Berry Allen.....	Dallas, Tex.
Michael Joseph Arden.....	New York, N. Y.
William Rankin Arrowsmith.....	New Orleans, La.
Henry Holmes Babcock.....	Providence, R. I.
Donald Church Balfour, Jr.....	Los Angeles, Calif.
HUGH D. BENNETT.....	Houston, Tex. (V.A.)
LEONIDAS HARRIS BERRY.....	Chicago, Ill.
GEORGE ISAAC BLUMSTEIN.....	Philadelphia, Pa.
Vernard Franklin Bond, Jr.....	Winston-Salem, N. C.
Howard Abner Boone.....	Memphis, Tenn.
Nathan Brown.....	Binghamton, N. Y.
Richard Henry Bruning.....	Maplewood, N. J.
Sidney Harold Burness.....	Hartford, Conn.
NORMAN BURNSTEIN.....	Jackson, Miss.
DOUGLAS GEORGE CAMERON.....	Montreal, Que., Can.
CHARLES SUMNER CAMPBELL.....	Salem, Ore.
Bruce Livingston Canaga, Jr.....	M.C., U. S. Navy
Lawrence Albert Cantow.....	Detroit, Mich.
Joseph Peter Carson.....	West Hartford, Conn.
WILLIAM ROBERT CARSON.....	Potsdam, N. Y.
Chester Cassel.....	Miami, Fla.
ELMER LEONARD CAVENY.....	M.C., U. S. Navy
FREDERIC DUNBAR CHAPMAN.....	Washington, D. C.

- RICHARD MORTON CHRISTIAN.....Greenwood, S. C.  
 William Stratton Clark.....Cleveland, Ohio  
 WALTER SLATER COE.....Louisville, Ky.  
 Lewis Cohen.....Detroit, Mich.  
 Louis Jack Cole.....Toronto, Ont., Can.  
 ELLISON RICHARDS COOK, III.....Savannah, Ga.  
 Henry Dale Cook.....Toledo, Ohio  
 James Randel Cook.....Cleveland, Ohio  
 Ernest Craige.....Chapel Hill, N. C.  
 Seymour Bernard Crepea.....Madison, Wis.  
 Alfred Eugene Cronkite.....Fort Lauderdale, Fla.  
 Ernest Whitaker Crow.....Wichita, Kans.  
 Edgar Lee Crumpacker.....White Sulphur Springs, W. Va.  
 WALTER SHELLEY CULPEPPER.....New Orleans, La.  
  
 Jacob Bernard Dana.....Togus, Maine (V.A.)  
 ROBERTS JUDSON DAVIES.....Seattle, Wash.  
 Frank Willard Davis, Jr.....Baltimore, Md.  
 Walter Grayburn Davis.....Denver, Colo.  
 Raymond Merrill deHay.....Lanikai, T. H.  
 LEWIS DICKAR.....Brooklyn, N. Y.  
 Lewis Jay Dimsdale.....Sioux City, Iowa  
 Casimir Anthony Domzalski.....Honolulu, T. H.  
 Jordan Hal Doran.....Indianapolis, Ind.  
 WILFRED DORFMAN.....Brooklyn, N. Y.  
 VIRGIL JACKSON DORSET.....Staten Island, N. Y. (U.S.P.H.S.)  
 Donn Raymond Driver.....Sioux Falls, S. D. (V.A.)  
 Jacob Louis Drossner.....Camden, N. J.  
 William Glenn Dunnington.....M.C., U. S. Army  
 Milton Dworin.....New Rochelle, N. Y.  
  
 Ellis Neil East.....Winnipeg, Man., Can.  
 JACK LANGOHR EISAMAN.....Bluffton, Ind.  
 LEONARD PAUL ELIEL.....Oklahoma City, Okla.  
 JOHN LESLIE ENYART.....M.C., U.S. Navy  
 Frederick Adams Erskine.....Richmond, Va. (V.A.)  
 HUGH STEWART ESPEY.....Quincy, Ill.  
  
 Robert John Fahey.....Boston, Mass.  
 Leonard Felder.....New York, N. Y.  
 JOEL FELDMAN.....Red Bank, N. J.  
 SAMUEL GUSTAV FEUER.....Brooklyn, N. Y.  
 LOUIS DAVID FEY.....Seattle, Wash.  
 Edward Elliot Fischel.....New York, N. Y.  
 GEORGE SEIBERT FISHER.....Detroit, Mich.  
 M(ARTIN) EUGENE FLIPSE.....Miami, Fla.  
 GEORGE WILLIAM FORMAN.....St. Joseph, Mo.  
 Joseph Kenneth Freilich.....Chicago, Ill.  
 Bernard M. Friedman.....Brooklyn, N. Y.  
  
 Sidney Clarence Garrison, Jr.....Murfreesboro, Tenn.  
 Robert Albert Gerisch.....Detroit, Mich.  
 William James Gleckler.....San Mateo, Calif.



Herbert Raymond Glodt.....	Pittsfield, Mass.
ALFRED FRANCIS GOGGIO.....	Berkeley, Calif.
JOHN JAMES GOLDSBERRY.....	Worcester, Mass.
Oscar Emanuel Goldstein.....	Passaic, N. J.
JOHN JOSEPH GRADY.....	Lakewood, Ohio
ROBERT LELAND GRIFFITH.....	Seattle, Wash. (U.S.P.H.S.)
Richard Putnam Gripe.....	Lafayette, Ind.
ROBERT LESLIE GRISSOM.....	Omaha, Nebr.
LUDWIK GROSS.....	New York, N. Y. (V.A.)
Murray Alan Grossman.....	Syracuse, N. Y.
Carl Joseph Gulotta.....	New Orleans, La.
LEONARD BERYL GUTNER.....	White Plains, N. Y.
WILLIAM REID HAAS.....	M.C., U. S. Air Force
James Stanford Haimsohn.....	Memphis, Tenn. (V.A.)
Diedrich Jansen Haines.....	Des Moines, Iowa
GEORGE CAVERNO HAM.....	Chapel Hill, N. C.
William Francis Hanisek.....	Easton, Pa.
Hugh Henderson Hanson.....	Houston, Tex.
BERNARD LAURISTON HARDIN, JR.....	Washington, D. C.
William Dale Harrelson.....	Kalamazoo, Mich.
John Ezra Harroun.....	Owosso, Mich.
Thomas Lees Hartman.....	Washington, D. C.
Reed Harwood.....	Boston, Mass.
ELMER WESLEY HEFFERNON.....	Boston, Mass.
John Daniel Helm, Jr.....	Lancaster, Pa.
Lawrence Melvin Herman.....	Monterey Park, Calif.
Melvin Hershkowitz.....	New York, N. Y.
John Arthur Hildes.....	Winnipeg, Man., Can.
E(DGAR) HAROLD HINMAN.....	San Juan, P. R.
Julian Bernard Hoffman.....	Brooklyn, N. Y.
IRVING NATHAN HOLTZMAN.....	Brooklyn, N. Y.
Robert Bruce Howard.....	Minneapolis, Minn.
FERDINAND JOSEPH HRUBY.....	Cleveland, Ohio
Rex Lamar Huff.....	Seattle, Wash. (V.A.)
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## OBITUARIES

## DR. HYMAN I. GOLDSTEIN

Dr. Hyman Isaac Goldstein (Associate) died of a heart attack in Philadelphia while attending a seminar at the Hospital of the University of Pennsylvania on March 17, 1954.

Dr. Goldstein was born in Baltimore, Md., Nov. 2, 1887. He received his M.D. degree from the University of Pennsylvania School of Medicine in 1909. He pursued postgraduate studies in both Vienna and Budapest. He practiced internal medicine and gastroenterology in Camden, N. J., until his death. He had been an Associate of the American College of Physicians since 1921, when he joined the American Congress on Internal Medicine.

He was Senior Physician, Deborah Sanatorium, Browns Mills. He was a member of the Medical Society of New Jersey, American Medical Association, American Trudeau Society, American Heart Association, National Gastroenterological Association, International Society of Internal Medicine, and the New Jersey Gastroenterological Society, of which he was a past President. He also was a member of the Philadelphia Pediatric Society, Medical Club of Philadelphia and B'nai B'rith. He was the author of numerous publications concerning gastroenterology and the history of medicine.

The passing of Dr. Goldstein will be mourned by his family, colleagues, patients and friends.

EDWARD C. KLEIN, JR., M.D., F.A.C.P.,  
Governor for New Jersey

## DR. E. RUSSELL ZEMP

Dr. Ernest Russell Zemp, F.A.C.P., died in Knoxville, Tenn., February 7, 1954, of a heart attack. He was 82 years old and had remained in active practice until two weeks before his last illness.

Dr. Zemp was born in Camden, S. C., receiving a B.S. degree from the South Carolina Military Academy in 1890 and his M.D. from the University of Maryland School of Medicine in 1894. He was married in 1898 to the former Katherine Hurst of Marion, Ala.

For a period of fifteen years he taught at the Lincoln Memorial University as Professor of Materia Medica, Therapeutics and Pediatrics, and Professor of Clinical Medicine.

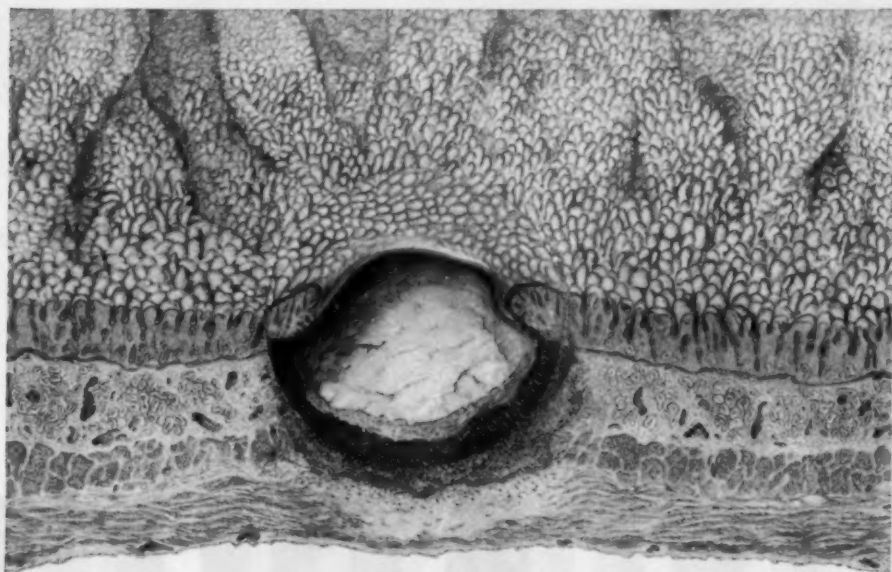
Dr. Zemp, described as a person of "rigid integrity" by his associates, practiced medicine in Knox County of Tennessee for sixty years. He became President of Knox County Medical Society, 1903; President of East Tennessee Medical Society, 1909; President of the Tennessee State Medical Association, 1928. He became a Fellow in the American College of Physicians in 1928. For twenty years he was Speaker of the House of Delegates of the Tennessee State Medical Association. It has been said of him that he knew every physician in his state, and certainly every physician in the state knew him and respected him for the years of hard work he gave to improve his profession.

He never missed a meeting of his Rotary Club for a period of fifteen years, and for many years he was present at every game the University of Tennessee football team played, no matter how far he had to travel over the country.

Not only was Dr. Zemp one of the oldest practicing physicians in Tennessee, but he took an active and enthusiastic part in everything that would improve conditions in the state and in his medical profession.

W. C. CHANEY, M.D., F.A.C.P.,  
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Cross section of active duodenal ulcer.

## Dramatic Remission of Ulcer Pain

*Pain of ulcer is associated with hypermotility; the pain is relieved when abnormal motility is controlled by Pro-Banthine.<sup>®</sup>*

"In studying<sup>1</sup> the mechanism of ulcer pain, it is obvious that there are at least two factors which must be considered: namely, hydrochloric acid and motility.

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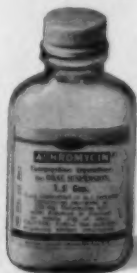
Pro-Banthine is proving equally effective in the relief of hypermotility of the large and small bowel, certain forms of pylorospasm, pancreatitis and ureteral and bladder spasm. G. D. Searle & Co., Research in the Service of Medicine.

1. Ruffin, J. M.; Baylin, G. J.; Legerton, C. W., Jr., and Texter, E. C., Jr.: Mechanism of Pain in Peptic Ulcer, *Gastroenterology* 23:252 (Feb.) 1953.

2. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, *Gastroenterology* 25:416 (Nov.) 1953.



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**ORAL SUSPENSION:** Cherry flavor.  
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Niacinamide.....	100 mg.
Calcium pantothenate.....	30 mg.
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Folic acid.....	1.5 mg.
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Bottles of 30 and 100.

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1 or 2 capsules daily.  
Bottles of 100 and 500.

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\*Therapeutic Nutrition, Committee on Therapeutic Nutrition, Food and Nutrition Board, Publication 234, National Research Council.

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1. Editorial, J. Allergy 23: 279, 1952.

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*large  
gastric ulcer*

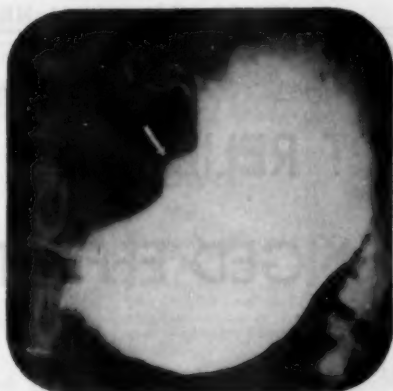


Fig. 3, Case 103 before therapy.

*healed  
with*



Fig. 6, Case 103 after 4 months PRANTAL therapy.

\* Heineken, T. S.: Rev. Gastroenterol. 20:829, 1953.

**PRANTAL**...relieves pain  
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widest variety of dosage forms

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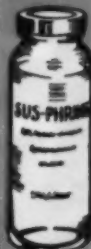
*Brewer*

for subcutaneous injection

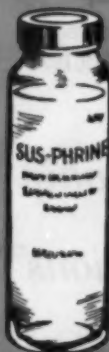
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2 cc. VIAL



3 vials to  
a package



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Jenkins, M. C. *Jl. National Med. Assoc.* 45:120, 1953.

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Naterman, H. L. *The Journ. of Allergy*. 24:40, 1953.

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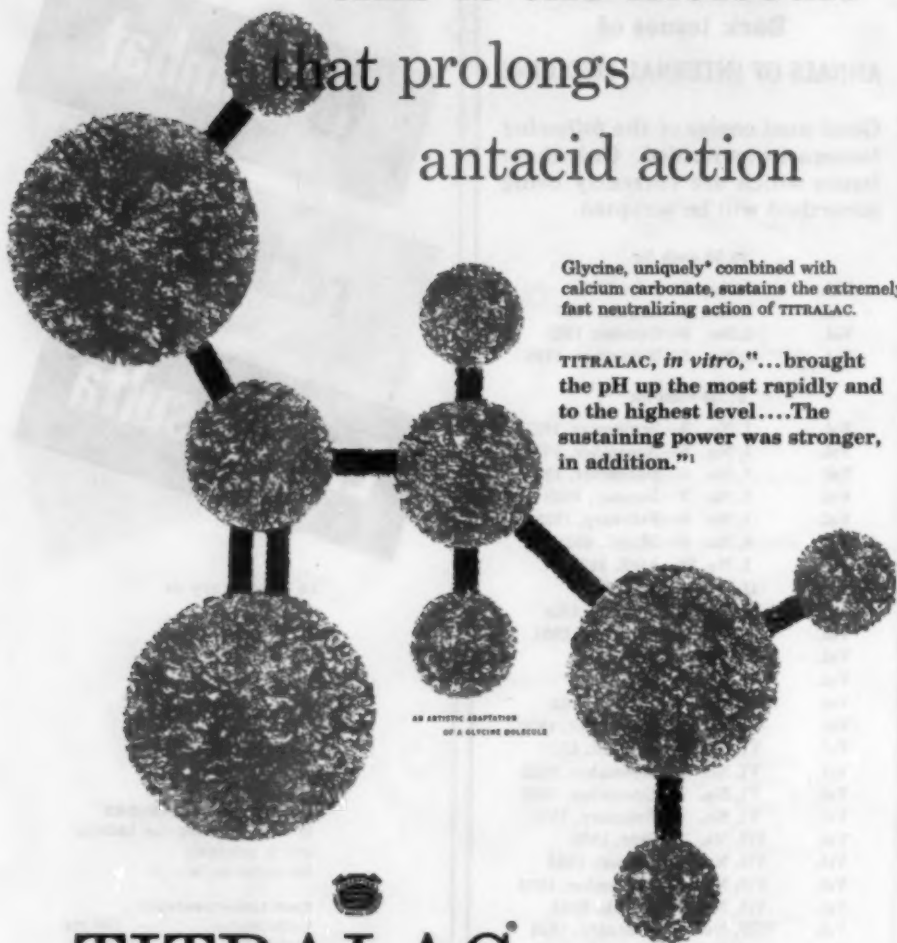
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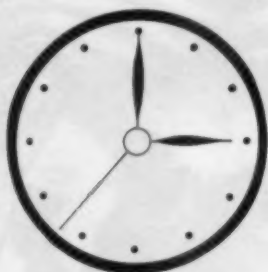
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